

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**AFFIDAVIT OF JOHN MARTIN LEONARD, M.D.**

I, John Martin Leonard, M.D., hereby declare and say:

1. My name is John Leonard. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

**Educational and Professional Background**

2. I am currently employed at Abbott Laboratories ("Abbott") as the Senior Vice-President of Global Pharmaceutical Research and Development.

3. I attended the University of Wisconsin and graduated in 1979 with a Bachelor of Arts degree in Biochemistry. I attended The John Hopkins University School of Medicine and graduated with an M.D. in 1983. I completed my medical internship and residency at Stanford University Hospital from 1983 to 1986. From 1986

to 1989 I was a postgraduate fellow in the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH). After I left the NIH in 1989, I briefly worked at G.H. Besselaar Associates, a contract research organization that conducted clinical trials.

4. I began working at Abbott in March 1992 as the Venture Head of the Anti-Viral Venture. In 1996, I became the Divisional Vice-President for anti-infective disease. I was promoted to Divisional Vice-President of Ventures in 1997 and, in 1999, I became the Corporate Vice-President for Development of Abbott's Pharmaceutical Products Division. In that position, I was responsible for the pharmaceutical development activities of that division. More specifically, I was responsible for supervising clinical work relating to oncology, neuroscience and anti-infective compounds under development. ABT-518, ABT-594, ABT-773 and ABT-492, among many other compounds, were within my area of responsibility. My responsibilities also included supervising some non-clinical activities, such as formulation of compounds, pre-clinical animal work as well as the statistics and data management group. In 2001, I became Corporate Vice-President for Global Pharmaceutical Development, also in the Pharmaceutical Products Division. Jeffrey Leiden, who joined Abbott in late 2000, was my immediate supervisor. In my various positions at Abbott, I have been responsible for conducting and/or supervising a substantial number of clinical trials on behalf of the company.

5. In 2004, I became the Corporate Vice-President of Global Medical and Scientific Affairs. I was promoted to Corporate Vice-President of Global Pharmaceutical Research and Development in April 2006, and recently promoted to Senior Vice-



President of Global Pharmaceutical Research and Development. In these positions, I headed and continue to head Abbott's Pharmaceutical Research and Development organization.

Abbott's Research and Development Process for New Therapeutic Drugs

6. Abbott is a global healthcare company. Its principal business is the discovery, development, manufacture and sale of a broad line of health-care products, including pharmaceuticals. Abbott's total expenditures for research & development for 2000 and 2001 were approximately \$1.246 billion and \$1.492 billion, respectively. Research and development expenditures have increased each year and currently exceed \$2.2 billion.

7. At Abbott, as with other major pharmaceutical companies, new therapeutic drugs in development typically go through three "phases" of clinical testing in humans after passing out of the discovery and pre-clinical phases. The discovery and pre-clinical phases of pharmaceutical research and development involve the identification of molecules that are candidates for clinical testing, their characterization in *in vitro* assays, both toxicological and metabolic testing, as well as the creation of a formulation suitable for subsequent human testing of the active ingredient. In Phase I of the clinical development process, testing is typically done on a relatively small number of human volunteers, who are generally healthy. The principal purpose of Phase I testing is gain early information on the safety and toxicity of compounds along with pharmacokinetic information to permit the selection of doses appropriate for testing in patients. In Phase II, the compounds are administered to patients afflicted with the condition that the drug is intended to treat. Unlike the trials in Phase I, Phase II trials are larger and typically

attempt to determine the efficacy in addition to the safety of a variety of doses. Phase II trials include dose-ranging trials to establish the doses that will be tested in subsequent pivotal trials in patients; additional dose-ranging work is often done in Phase III clinical trials. During Phase III, the last phase of clinical development done before Abbott, like other drug sponsors, seeks regulatory approval for the new drug, the size of the clinical trials is significantly increased and the focus of the research is to confirm the efficacy and safety of the drug at the intended final dose or doses in the final patient population. If the new drug passes successfully through the three principal phases of clinical development, Abbott's clinical research and regulatory affairs teams will prepare a New Drug Application ("NDA") for the FDA's review. If the FDA approves the NDA, the new drug may be brought to market in the United States.

Negotiation of the RFA and Creation of the Descriptive Memoranda

8. I was informed in early 2000, in my role as Corporate Vice-President for Development that Abbott Laboratories was negotiating a contract with John Hancock Life Insurance Company ("Hancock") for the purpose of acquiring additional funding to share the cost of developing several of Abbott's key pre-clinical and clinical compounds. I was enthusiastic about partnering with Hancock because I believed that the shared development strategy would be advantageous for both Abbott and our future partner.

9. I was not directly involved in the negotiation of the terms of the research funding agreement ("RFA") between Abbott and Hancock. I am aware that the RFA provided that Hancock would contribute funding for nine pharmaceutical compounds (the "Program Compounds") including ABT-518, ABT-594, and ABT-773. As discussed above, as Corporate Vice-President of Development for Abbott's Pharmaceutical

Products Division, I was responsible for the development of these three compounds in 2000, and in 2001 when I was promoted to Corporate Vice-President for Global Pharmaceutical Development. I was aware at that time of the general development status and prospects for ABT-518, ABT-594, and ABT-773.

10. In July 2000, before the RFA was executed, I participated in a telephone call with Mr. Stephen Cohen of Abbott, Mr. Stephen Blewitt of Hancock and Dr. Lynn Klotz, who I understood was an independent scientific consultant retained by Hancock to assist Hancock's due diligence with regard to the compounds. During this call, I answered several questions posed by Dr. Klotz and Mr. Blewitt regarding the development status of many of the Program Compounds. Most of the questions were posed to me by Dr. Klotz. I attempted to answer all of the questions, based on my personal knowledge regarding the Program Compounds. Although I do not recall the specifics of the discussions, I have a general recollection that we discussed the side effect profile of ABT-594. At that time I understood that the dose limiting side effects were not dangerous, like hypothermia and seizures, but less severe, including headaches and vomiting. As discussed below, these side effects were also disclosed in the versions of the descriptive memoranda we gave to John Hancock.

11. The RFA included Descriptive Memoranda that were included as exhibits to the RFA. They were drafted at the direction of Steve Cohen, the controller of the Pharmaceutical Products Division Research and Development Group. I did not draft the Descriptive Memoranda that were included with the RFA. They were drafted by individuals in New Product Development and the respective heads of the teams developing the compounds that are the subject of the memoranda. Members of the

development teams for each of the various compounds were primarily responsible for reviewing and modifying the Descriptive Memorandum for their respective compounds.

12. I reviewed earlier drafts of some of the Descriptive Memoranda and Annual Research Plans, including the November 2000 Descriptive Memoranda. Attached hereto as D's Exhibit A are true and correct copies of the November 2000 Descriptive Memoranda and Annual Research Plans for ABT-518, ABT-594, and ABT-773 with my handwritten notes on the documents. As set forth in my notes, after reviewing the draft Descriptive Memoranda and Annual Research Plans, I concluded that they were well written and would provide Hancock with the information that it wanted. *Id.* at ABBT0006628. I also reviewed each of the final February 2001 Descriptive Memoranda before the RFA was executed.

13. My purpose in reviewing the Descriptive Memoranda was to confirm the accuracy of the information contained within them. If I determined, based on information that I had received regarding the Program Compounds, that anything included in the draft Descriptive Memoranda that I reviewed was inaccurate, I either reported the inaccuracy to the individual responsible for drafting the Descriptive Memoranda in order to have it corrected or I annotated the document itself for correction. For example, I noticed with regard to the Descriptive Memorandum for ABT-518 that the draft Descriptive Memorandum stated that the Phase I clinical trial for ABT-518 started in December 2000. By the time I reviewed this draft memorandum, the beginning of this trial had actually been pushed back to March 2001. Accordingly, I noted the need to correct this information in the Descriptive Memorandum before the RFA was executed.

14. I am aware that ABT-980 was one of the compounds that was originally planned to be included as a Program Compound in 2000 the RFA during early negotiations. During 2000, we became aware for the first time of a safety issue regarding ABT-980. We discussed this previously unobserved safety issue internally for several weeks, and consulted independent experts about our concerns. Ultimately, as a result of these safety concerns, we decided to discontinue development of the compound. I understand that Hancock was notified of the termination and the parties agreed to replace it with other compounds.

#### ABT-518

15. In 2000 and 2001, I was generally responsible for the development of ABT-518. I was kept informed of the development of that compound by Dr. Perry Nisen, the Vice-President of Oncology Development, who reported directly to me, and Dr. Azmi Nabulsi, the Venture Head for the Oncology Venture, who reported to Dr. Nisen. In 2000 and 2001, I met and corresponded frequently with Dr. Nisen, Dr. Nabulsi, and other members of the ABT-518 development team to discuss the status and the ongoing clinical trial for the compound and I attended several executive-level meetings during which the status of ABT-518 was discussed. I also received the monthly status project reports created by the ABT-518 development team during this period.

16. ABT-518 is a oncological pharmaceutical compound that was under development at Abbott in 2000 and 2001. It belongs to a novel class of compounds known as Matrix Metalloproteinase Inhibitors (“MMPi”). Matrix Metalloproteinases (“MMPs”) are a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with

tumor growth. At the time of the agreement with Hancock, within Abbott's oncology venture, and the oncology field in general, it was hypothesized that inhibition of certain MMPs would inhibit tumor progression. Based on the preclinical work that Abbott had performed, we believed ABT-518 had certain potential advantages over other MMPIs. ABT-518 was highly selective for inhibition of two particular MMPs, gelatinase A and B, which were believed to play a particularly important role in tumor progression. Other MMPI compounds under development by Abbott's competitors — such as Pfizer's compound Prinomastat, and British Biotech's compound, Marimastat — were less selective in inhibition of these particular enzymes, although Prinomastat was moderately selective and most similar to ABT-518 in that regard. Therefore, we believed that ABT-518 might be more efficacious in inhibiting tumor progression. In addition, the competitors' MMPI compounds had exhibited side effects characterized by joint pain and stiffness ("joint effects" or "joint toxicity") in clinical trials, which limited the doses at which they could be administered. We hypothesized that these joint effects were caused by inhibition of MMPs other than gelatinase A and B, such as fibroblast collagenase. Because of ABT-518's greater selectivity, we believed that ABT-518 was less likely to cause joint toxicity, and that we might therefore be able to administer at higher doses that would be more efficacious. In addition, because of ABT-518's unique pharmacological properties, our preclinical work suggested that it could achieve more sustained and consistent potency, which might also allow greater efficacy without the need for dosing at levels that might cause greater toxicity.

17. As reflected in the first Annual Research Plan for ABT-518 that was provided to Hancock as part of the Agreement, from the beginning of the development of

ABT-518 through 2000 we had spent \$40 million on developing the compound.

Attached hereto as D's Exhibit Y is a true and correct copy of the Research Funding Agreement dated March 13, 2001, which reflects Abbott's spending through 2000 at page JH008127.

18. The final Descriptive Memorandum for ABT-518, which I reviewed as discussed above and which was provided to Hancock as part of the Agreement, disclosed that "Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases." D's Exhibit Y at JH008194. The Descriptive Memorandum also disclosed the problems experienced by competitor pharmaceutical companies' MMPIs including that (1) Marimastat had shown "no survival advantage [in pancreatic cancer]" and that other MMPI compounds had not demonstrated efficacy; (2) the competitor compounds, including Marimastat and Prinomastat, had "dose limiting toxicity" that "almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy"; and (3) "Bayer recently dropped development" of its MMPI compound due to concerns about potential toxicity. *Id.* at JH008197-99. The Descriptive Memorandum also states that because ABT-518 was at a less advanced stage of development the "[side effect] hurdles will be even higher for this compound." *Id.* The Descriptive Memorandum also disclosed:

As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

*Id.* at JH008199. I believed at the time that I reviewed the final Descriptive

Memorandum for ABT-518 and when it was provided to Hancock in March 2001 that it was accurate and contained the information necessary to accurately convey the condition of and prospects for the ABT-518 program.

19. Based on the information that was provided to me by members of the ABT-518 development team, I was optimistic in March 2001 about the prospects for development of ABT-518. I remained optimistic about ABT-518 into May 2001. During that month, at the American Society of Clinical Oncology (“ASCO”) conference, we received newly-disclosed clinical trial data regarding certain MMPI compounds developed by other pharmaceutical companies that was pertinent to ABT-518. MMPIs were a novel pharmacology and no MMPI compound had successfully completed phase III trials or gained regulatory approval as of early to mid-2001. While we were optimistic about the MMPI program, it was an early-stage program in a novel class of compounds.

20. As discussed above, prior to May 2001, based on the limited information we had, I believed that Abbott had an opportunity to be successful where several of our competitors had not been successful because the pre-clinical work we had done to that point promised the possibility of developing a compound that had a selectivity profile that would inhibit the appropriate target MMP enzymes, gelatinase A and B, while not affecting other MMPs implicated in the toxicity observed in prior clinical tests. In other words, again based on the limited information available to us, I believed that ABT-518 was sufficiently different from its potential competitors that it had a good chance of avoiding the difficulties that we understood other pharmaceutical companies had apparently encountered with their MMPIs. My view in this regard was based on information provided to me by the ABT-518 development team.



March 7-9, 2001 Portfolio Review Meeting

21. At the end of 2000, Abbott acquired the Knoll Pharmaceutical Division of BASF Corporation, together with compounds that Knoll was developing. On March 7-9, 2001, I attended a series of meetings regarding the pharmaceutical compounds in Abbott's portfolio and in the newly acquired Knoll portfolio as part of a portfolio review. The meetings were held at the Deerfield Hyatt Regency. Attached hereto as D's Exhibit 621 is a true and correct copy of the final schedule for the portfolio review that I received prior to the portfolio review. The purpose of the March 2001 Portfolio Review Meeting was to examine the technical, scientific, medical and commercial status of Abbott's pre-acquisition compounds and the compounds acquired through the Knoll acquisition.

22. During the Portfolio Review Meeting, Dr. Nisen gave a short presentation regarding ABT-518. I attended the presentation regarding ABT-518 and am familiar with the slides that Dr. Nisen included in that presentation. Attached hereto as D's Exhibit 782 is a true and correct copy of the slides presented during Dr. Nisen's ABT-518 presentation. As stated in the slides, the ABT-518 development team believed that there was "no joint-toxicity expected" with respect to ABT-518. In this respect we believed ABT-518 had a potential advantage over competitors' MMPI compounds, which had exhibited side effects of musculoskeletal pain and stiffness in the joints ("joint effects" or "joint toxicity"). As stated in the slides, we also believed that ABT-518 was "[h]ighly selective for the inhibition of gelatinases A & B" (which play a role in tumor progression), "very potent", and "potentially best in class." Although we believed at the time these properties of ABT-518 would give it an advantage over other compounds, we did not have sufficient data to know that ABT-518 would succeed in clinical testing or

differentiate from competitor compounds with any certainty. Thus, the slides presented by Dr. Nisen noted that “competitor data may pose additional development hurdles.” *Id.* at ABBT0064326. The information Dr. Nisen presented regarding ABT-518 at the Portfolio Review Meeting accurately reflected the state of our knowledge about ABT-518 and about competitors’ MMPI compounds at that time.

23. Shortly after Dr. Nisen gave his presentation on ABT-518 at the March 2001 Portfolio Review Meeting, I attended a much smaller, executive level meeting with Dr. Leiden and others. During that meeting, Dr. Leiden issued a directive to put a temporary hold on the Phase I M00-235 clinical trial of ABT-518, which was the “first in man” study of the compound. Dr. Leiden said that he wanted to wait until after the May 2001 ASCO conference before enrolling patients in this trial. At that conference, competitors were expected to release recent detailed clinical data regarding their MMPI compounds. Dr. Leiden stated that he wanted us to be able to analyze that data and its implications for the development of ABT-518 before continuing with the M00-235 trial and incurring additional expenses. At the time Dr. Leiden issued this temporary hold directive, enrollment had begun for the M00-235 trial.

24. Since Dr. Leiden had only recently joined Abbott, he was not familiar with the details of the ABT-518 program at the time of the March 2001 Portfolio Review Meeting. Those of us who were more familiar as of March 2001 with ABT-518 than Dr. Leiden, including myself and Dr. Nisen, disagreed with his decision to put a temporary hold on beginning the M00-235 clinical trial.

25. After the meeting discussed above, during which Dr. Leiden informed us that the clinical trial would be put on a temporary hold, I had a follow-up conversation

with Dr. Leiden during which I explained to him why I believed the hold on the ABT-518 clinical trial should be lifted. I emphasized that the ABT-518 discovery and development teams advanced the drug based on pre-clinical data distinguishing it from competitor drugs. Furthermore, I explained our hypothesis that these pre-clinical differences might lead to meaningful clinical differences in clinical trials in patients. I suggested that we should not delay the ABT-518 clinical trial while waiting for release of data regarding other MMPI compounds because even if that data was negative, it might not bear directly on ABT-518. I pointed out that a delay in the clinical trial could later put Abbott at a competitive disadvantage if we continued development after the ASCO conference. I also informed Dr. Leiden that the amount of money we would save on the clinical trial was relatively minor compared to the value to Abbott that would be lost if the launch of the compound was delayed. I also recall reminding Dr. Leiden that Hancock was a partner for ABT-518 because I thought it might alleviate some of his concerns regarding the financial risks of continuing with the development of the compound without waiting for the ASCO results.

26. A short time after Dr. Leiden had placed the hold on the clinical trial for ABT-518, he informed us that he had reversed his decision and that he had lifted the temporary hold on the clinical trial. Given the short time that the hold was in place and the fact that the clinical trial did, in fact, continue after the hold was lifted, I did not believe at the time, nor do I believe now, that the temporary hold had a material impact on Abbott's development of ABT-518 or on the prospects for the compound's success.

27. I attended a Prioritization Review during the first week of May 2001 that was chaired by Dr. Leiden. The May Portfolio Prioritization was designed to examine

the medical needs in particular therapeutic areas and to determine what opportunities may exist for Abbott in those areas. I attended the presentation given by the Oncology Venture during the early May Prioritization Review. Since the data from the ASCO conference was not yet available, we did not make a decision regarding ABT-518 during that Prioritization Review. Attached hereto as D's Exhibit 755 is a true and correct copy of the Oncology Venture presentation given during the May 2001 Portfolio Review. As reflected in the document, the presentation by the Oncology Venture was a general overview of the venture's work and did not include any new information about ABT-518, since the May 12-15, 2001 ASCO conference had not yet taken place. I have no recollection that there was any discussion at the early May retreat about the temporary hold that Dr. Leiden had placed on the M00-235 trial in March or of his decision to lift that temporary hold. Nor do I remember any discussion about the possibility of terminating ABT-518.

#### ASCO Results and Discontinuation of ABT-518

28. Prior to the ASCO conference, we had only very limited information from publicly available sources, such as press releases, regarding some of the recent competitors' trials of MMPI compounds. For example, attached hereto as Exhibit FL is a true and correct copy of an email produced from Abbott's files with an August 7, 2000 press release from Pfizer announcing that it was halting Phase III trials of Prinomastat in combination with standard chemotherapy in patients with non-small cell lung cancer and advanced hormone refractory prostate cancer because they "did not meet primary efficacy objectives" and that "neither detrimental nor convincing beneficial effect was observed." The press release noted that Pfizer "intends to continue exploration of

Prinomastat in other tumor types and, most importantly, in earlier stage disease, where oncologists believe inhibition of angiogenesis may have greater utility.” The release also noted that “four phase II trials are currently underway and two additional phase II trials will begin shortly.” We could not make any determination from press releases and other publicly available reports, however, regarding the potential impact of this information regarding competitor’s trials on ABT-518. For example, the press reports did not identify what “primary efficacy objectives” were being measured in the clinical trials of Prinomastat or disclose whether the trials also measured achievement of secondary efficacy objectives, which could be important in analyzing whether there were signals of efficacy in more sensitive efficacy end points. Nor did the press reports provide other essential details of the studies, such as sample size, disease stage and other patient characteristics. In order to make a determination regarding the potential significance of the competitors’ trials with respect to ABT-518, it was essential for us to review and analyze the peer-reviewed reports of the actual clinical data, which was released at ASCO.

29. ASCO is the leading clinical oncologic group in the United States and its yearly conference is probably the most important oncology conference in the world. Abbott employees attend the ASCO conference each year, in part to learn new information about developments in the field, including peer-reviewed reports of new clinical data regarding oncology compounds in development by other companies. I understand that ASCO rules provide that presentations at the conference cannot include previously released data, therefore, by necessity, all the data released at ASCO each year is new.

30. Dr. Nisen, Dr. Nabulsi, Dr. Davidsen, and other Abbott employees attended the May 12-15, 2001 ASCO conference. As discussed above, since we were in the midst of the ABT-518 development program in 2001, we were particularly interested in the information about MMPIs that would be presented during the conference. We were aware that other pharmaceutical companies would be presenting significant amounts of previously unavailable clinical trial data at that conference regarding their respective MMPI programs. We expected that multiple competitors to reveal their detailed results regarding studies of various MMPI compounds with differing properties and toxicity profiles tested on multiple tumor types under a variety of different circumstances, including in combination with other treatments and as stand-alone (i.e., “mono”) therapy and in advanced Phase III trials. As we had discussed in meetings at Abbott prior to the conference, we believed the information that would be disclosed during the ASCO conference would be instrumental in allowing us to make an informed decision regarding the development of ABT-518.

31. On May 22, 2001, I received from Dr. Nisen a summary of the findings on competitors’ MMPIs that had been presented at the May 2001 ASCO conference and the ABT-518 project team’s recommendations regarding ABT-518, based on this new information. Attached hereto as D’s Exhibit 586 is a true and correct copy of the 2001 ASCO MMPI Update that I received from Dr. Nisen. On or around May 28, 2001, I attended a presentation at Abbott made by Dr. Nisen that summarized the MMPI competitor clinical trial data that was released during the conference. Dr. Nisen also provided additional details regarding the clinical trial in an oral presentation and question and answer session that accompanied his report.

32. Attached hereto as D's Exhibits FI, 793, and FK are true and correct copies of documents I recognize to be abstracts and posters from the 2001 ASCO conference, which were summarized in Dr. Nisen's report. As reflected in the abstracts, more detailed data was released at ASCO than had previously been available. For example, as reflected in D's Exhibit 793 at ABBT0556352, Pfizer's abstract for its Phase III prostate cancer trial for Prinomastat reports the large size of the study ("553 [patients] were enrolled; interim results were available for 406 [patients]"), the characteristics of the patients with respect to age and disease severity ("balanced with median age 71 years, median PSA 94 ng/mL and 33% measurable disease"). ("PSA" stands for prostate specific antigen, which is a protein measured to track disease progression.) The abstract also reports that in the Prinomastat prostate cancer trial "Grade-2 MS [musculoskeletal effects] were observed in 13, 22, and 22% of the [patients] in the placebo, 5 and 10 mg arms, respectively." While Pfizer had previously reported merely that "primary efficacy objectives were not met" in its study of Prinomastat in prostate study cancer patients, in the ASCO abstract it reported the results of the specific primary and secondary endpoints ("[n]o differences were observed among the treatment arms in PSA response rate (RR, 75% reduction for 3wks), progression-free survival by radiography (RPFS), PSA (50% increase for 3wks), or symptoms (SPFS); or overall (OS) and 1-year survival").

33. With respect to Pfizer's Phase III trial of Prinomastat in patients with non-small cell lung cancer study, as reflected in D's Exhibit 793, the abstract reported the large size of the study ("686 [patients] were enrolled; interim results are available for 677 [patients]"), the characteristics of the patients with respect to age, sex, disease severity, and type of tumor ("balanced with median age 62 years, 62% male, 85% WHO PS 0/1 [a

measurement of disease severity], 56% adenocarcinoma [a type of tumor], 12.6% stage IIIB(T4), 74% stage IV, 11.8% recurrent disease, and 84% measurable disease”). *Id.* at ABBT0556350. It reported the joint toxicity experienced by treatment group (“Grade-2 [musculoskeletal] events occurred in 16, 19, 22, and 31% of [patients] in placebo, 5, 10, and 15 mg arms, respectively”). Finally, while Pfizer’s press release had merely reported that “primary efficacy objectives were not met”, the abstract reported the results with respect to specific primary and secondary endpoints (“[n]o differences were observed among the treatment arms in overall (OS) or 1-year survival, progression-free survival (PFS), symptomatic PFS (SPFS) or response rate”). *Id.*

34. As reflected in D’s Exhibits FK and FI, Pfizer also published at ASCO the clinical data from a smaller, earlier phase trial of 44 patients with metastatic breast cancer. Even though this trial included a higher 25 mg BID dose, as well as a 5 mg dose, Pfizer reported that “[n]o objective disease responses were observed” and that “[m]edian [time-to-progression] was 8 weeks in both arms”. D’s Exhibit FK at ABBT0556332; D’s Exhibit FI at ABBT0556331.

35. Bayer and British Biotech also reported negative results at ASCO in trials of their compounds, BAY 12-9566 and Marimastat. For example, as reflected in D’s Exhibit 793, Bayer released clinical data from a study of 243 patients, which showed “no evidence of an impact of BAY [12-9566] on [progression-free survival or [overall survival]].” *Id.* at ABBTABBT0556354.

36. After we reviewed the new information about MMPIs that was disclosed at ASCO, we concluded that Abbott should not continue with the development of ABT-518. The clinical trial data released at ASCO, involving a variety of compounds, tumor



types, patient characteristics, disease severity, combination therapy and mono therapy, failed to show significant signals of efficacy. The clinical data released at ASCO regarding Prinomastat was particularly significant, because Prinomastat overlapped with ABT-518 in terms of its selectivity for gelatinase A and B, and was tested in large scale advanced clinical trials. The key finding, based upon the ASCO data, was that MMPi's were less likely to demonstrate efficacy than we had hypothesized. In addition, in light of the additional data regarding joint toxicity experienced by competitors, there remained uncertainty regarding whether ABT-518, despite its different characteristics, would be able to avoid these problems. I concluded based on the clinical data that was disclosed at ASCO, particularly the lack of significant signals of efficacy, that it was much less likely that we would be able to successfully develop ABT-518. Some members of ABT-518's oncology team, including Dr. Nisen, advocated continuing clinical trials to test whether ABT-518, despite the negative data released at ASCO, might still be able to distinguish itself from the other competitors. I believed, however, that in light of the overwhelming negative data released at ASCO, the chances of success were too low to justify continuation of funding for development of ABT-518 at that time. I therefore concurred in the decision made by the Pharmaceutical Executive Committee ("PEC") shortly after the May 28, 2001 presentation by Dr. Nisen, that Abbott should not proceed with the compound.

37. Even though we had decided to terminate the ABT-518 program, we had an ethical obligation to the patients already enrolled in the M00-235 clinical trial. Therefore, we decided to allow the patients that were already enrolled in the clinical trial to complete the trial.

Out-Licensing of ABT-518

38. After we decided to terminate the development program of ABT-518 in late May or early June 2001, I encouraged Abbott's business development team to look for potential out-licensees or support for co-development of the compound. While I was not personally involved in the effort to out-license the compound, I was aware that it was ongoing. For example, I was informed that we made a presentation to Goodwin Philanthropy in an attempt to interest that organization in funding additional clinical trials for ABT-518. Attached hereto as D's Exhibit DT is a true and correct copy of the email exchange between Dr. Leiden and Dr. Nisen that was forwarded to me regarding the draft presentation for Goodwin Philanthropy.

39. I was generally aware of the out-licensing efforts of the business development team for ABT-518. I learned that the team had contacted and provided information about the compound to several pharmaceutical companies, including Chiron, Paramount Capital, Salmedix, and Sunesis, as well as Duke University. I was informed that the companies had no interest in licensing ABT-518 from Abbott.

ABT-594

40. In 2000 and 2001, I was generally responsible for the development of ABT-594. I was kept informed of the development of that compound by Dr. Chris Silber and Dr. Bruce McCarthy during that time period. Dr. Silber was the Venture Head of the Analgesia Venture until February or March 2001 when Dr. McCarthy was promoted to Venture Head. During the earlier time period, Dr. McCarthy was the medical director of the ABT-594 development team. In 2000 and 2001, I often met and corresponded with Dr. Silber, Dr. McCarthy, and other members of the ABT-594 development team to

discuss the status and the ongoing clinical trials for the compound. I also attended several executive-level meetings during which the status of ABT-594 was discussed. I also received the monthly status project reports created by the development team during this time period.

41. ABT-594 is a pharmaceutical compound that was under development in the Analgesia Venture at Abbott from 1997 through October 2001. As reflected in the first Annual Research Plan that was provided to Hancock, through 2000, Abbott had spent \$97.3 million developing ABT-594. D's Exhibit Y at JH008121.

42. ABT-594 falls within the class of pharmaceutical compounds known as cholergeric channel modulators ("CCM") or neuronal nicotinic receptors ("NNR"). Nicotine, the active agent in cigarettes, has been shown to have activity in psychosis, analgesia, cognition, depression, and a variety of other potential disease states. In an attempt to build on the observations that had been made over the years about the pharmacology associated with nicotine, Abbott had a long-standing NNR project that attempted to get the desired effects of nicotine without using nicotine itself and to develop compounds that did not exhibit the typical side effects of nicotine, namely, dizziness and nausea.

43. As discussed above, I reviewed the final Descriptive Memoranda that were provided to Hancock in March 2001 as part of the Agreement. The final Descriptive Memorandum for ABT-594 that I reviewed and that was provided to Hancock disclosed that the likelihood of ABT-594 reaching its target profile of low nausea/vomiting was "Low". D's Exhibit Y at JH008172. It also disclosed that during previous clinical trials, the "most common adverse events for subjects receiving 75 ug

[micrograms] BID [twice-a-day] were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).” *Id.* at JH008171. The Descriptive Memorandum further disclosed that the therapeutic window (i.e., the ratio between the maximum tolerated dose and the minimum efficacious dose) might be small because the Phase IIa studies “suggest a trend towards analgesic effect [efficacy]” at 75 micrograms twice-a-day and the Phase I studies indicated that the maximum tolerated dose might be as low as 150 micrograms per day). *Id.* at JH 008171. The Descriptive Memorandum also disclosed that a Go/No Go decision for clinical efficacy was expected in June 2001 at the conclusion of the Phase IIb (dose-ranging) trial (“M99-114”). *Id.* at JH008166.

#### M99-114 Trial

44. By 2000 the ABT-594 development team had completed a number of Phase I and small Phase II clinical trials. In April 2000, we initiated the Phase IIb M99-114 clinical trial for the treatment of painful diabetic neuropathic pain. The M99-114 trial was a dose-ranging study designed to determine the therapeutic index for ABT-594. The therapeutic index for a pharmaceutical compound is the relationship between the lowest dose that demonstrates efficacy and the highest dose that has an acceptable side effect profile. While there were other clinical trials planned for ABT-594, the M99-114 dose-ranging study was a necessary precursor to the additional clinical trials that were to be conducted for the compound. The M99-114 trial was designed with four different arms or dose groups: placebo, 150 mcg BID, 225 mcg BID, and 300 mcg BID. The primary purpose of the study was to determine a dose-response curve; this entails selecting a range of ascending doses to establish the safety and efficacy associated with each dose. High doses are selected with the intention of identifying a maximal dose either

by demonstrating no further gain in efficacy or finding unacceptable adverse events irrespective of the efficacy. We expected that at the higher doses there would be more drop-outs from side effects than at lower doses because the higher doses had been selected specifically to define an adverse event profile for the compound.

45. The M99-114 clinical trial was double-blinded and placebo controlled. A double-blinded, placebo-controlled clinical trial is one in which neither patients nor physicians know which dose of drug, if any, is being administered to each patient. The sponsor of a double-blinded, placebo-controlled trial, such as Abbott in the case of the M99-114 study, is also unaware of what dose is being administered to each patient.

46. Based on the earlier clinical trials conducted for ABT-594, we knew that the main dose-limiting side effects of ABT-594 were nausea, vomiting and dizziness. However, it was unclear whether there was a dose of ABT-594 that would be both efficacious and sufficiently well-tolerated to be a viable drug. The purpose of M99-114 was to determine if a dose with adequate efficacy and an acceptable side effect profile existed. During the M99-114 clinical trial, we learned before the data was unblinded that there were a number of patients who dropped out of the trial due to side effects. The fact that there were drop-outs as a result of side-effects was not unexpected, since the trial had been designed to determine the dose-limiting side effects. Moreover, we could not know before the data was unblinded whether the drop-out rate indicated that the therapeutic window for the drug would be too narrow for the drug to be commercially viable because, before unblinding, we did not, and could not know at what doses the drop-outs were occurring. We believed at the time, for example, that it was possible that

the adverse side effects were occurring at the highest doses and the lowest dose of 150 mcg would likely be both efficacious and well tolerated.

47. In late 2000, I became aware that we were experiencing slower enrollment in the M99-114 trial than we had expected and planned. As a result of this enrollment rate, the ABT-594 project team assessed whether we could still achieve our clinical goals for the M99-114 trial if we enrolled fewer than the originally targeted number of patients. I was kept informed of the analysis and was personally involved in reviewing the team's assessment. For example, attached hereto as D's Exhibit DB is a true and correct copy of a notice of a December 11, 2000 meeting that I attended with Chris Silber and David Morris, one of the Abbott statisticians working on the M99-114 trial, in order to discuss the power calculations for the M99-114 clinical trial. Based on all the information provided to me by the ABT-594 team, I made the decision to stop enrollment in the M99-114 trial before the trial achieved the original target number of patients. I made this decision because I had been informed and I had concluded that stopping enrollment at a smaller number than originally planned would not negatively affect in a meaningful way our ability to have a successful trial that would provide us with sufficient information to make an informed decision on the future of the product. I was informed by the clinical statisticians, for example, that they believed that the trial would likely reach a statistically significant endpoint with the number of patients that we had already enrolled in the trial. Based on this information provided to me by the ABT-594 team, and my experience with clinical trials, I concluded that we would gain little incremental information from reaching the target enrollment number than we would gain from the enrollment we had already achieved, and that the further delay and expense that would be caused by

attempting to reach the original enrollment goal was unwarranted. My decision in this regard was informed by the fact that, while we always try to enroll the target number of patients in a clinical trial, it is not uncommon, especially in the case of larger clinical trials such as M99-114, that we do not reach that target number and yet we are still able to achieve a statistically significant result that we are able to use in making decisions about the future of our products.

48. I was aware in late 2000 of efforts to explore a potential partnership with other pharmaceutical companies to co-develop ABT-594. The decision to seek a potential partnership was to gain additional resources to help fund the development of ABT-594 and maximize the value of the compound to Abbott and was not based on any belief that the compound would be discontinued. We would not have sought additional funding to co-develop ABT-594 and continued to spend millions of dollars of Abbott's research and development budget on the development of the compound if we believed that we were going to discontinue the development of the compound.

49. I am aware that Hancock has claimed that the fact that the clinical study report for the M99-114 clinical trial contains a statement that there were "significant changes in the developmental strategy" for the compound indicates that Abbott had decided to discontinue the development of the compound even before the M99-114 trial was completed. Hancock's contention is incorrect. No significant changes were made to the developmental strategy for ABT-594 until after the results of the M99-114 clinical trial was unblinded and the results of that trial were analyzed by the ABT-594 development team and senior management in the summer and early Fall of 2001.

50. In early 2001, at the end of the enrollment of the M99-114 clinical trial, we were still very optimistic about the prospects of ABT-594 and considered ABT-594 to be among our top ten development prospects in January 2001. For example, the company's January 2001 portfolio analysis review material notes that we considered ABT-594 one of our top four projects -- the same place it held in our July 2000 analysis. Attached hereto as D's Exhibit 750 is a true and correct copy of the January 2001 Review Reference Materials. *Id.* at ABBT0012382.

51. On February 2, 2001, I attended an ABT-594 Project Review presentation that was given to update the PEC on the status of the ABT-594 development program. Attached hereto as D's Exhibit 748 is a true and correct copy of the slides from that presentation. As reflected in the presentation, as of February 2, 2001, we believed that ABT-594 would be "First-in-class". *Id.* at ABBT0002361. The presentation also reflects that enrollment in the M99-114 clinical trial ended on January 5, 2001 with 269 patients and that the width of confidence intervals was not meaningfully different going from 269 to 320 patients (the target enrollment number). *Id.* at ABBT0002433. As we had determined in the fall of 2000, the difference between 269 and 320 patients was not significant in terms of our confidence in achieving statistically significant results for the trial. I do not remember any discussion during that presentation of blinded data from the trial or of the drop-out rate of the trial. Nor do I remember anyone who attended the presentation expressing concern that ABT-594 would not be a successful compound based on that clinical trial.

52. Prior to the unblinding of the data from the M99-114 trial, we did not know whether there was a dose at which the compound would be both efficacious and



have an acceptable side effect profile. We did not know prior to the unblinding of the M99-114 trial whether the drop-out rate for the M99-114 trial meant that the product would not be successful or that ABT-594 would be a “probable terminate”. I had not made any such determination personally and no one at Abbott ever informed me that they or anyone else had done so.

March 7-9, 2001 Portfolio Review Meeting

53. I attended the ABT-594 presentation by Dr. McCarthy during the off-site Portfolio Review Meeting on March 7-9, 2001. Attached hereto as D’s Exhibit 620 is a true and correct copy of the slides for ABT-594 presented during the portfolio review. I do not recall any discussion during the ABT-594 presentation regarding the drop-out rates for the ongoing M99-114 trial and at no point during that presentation did we come to a consensus that ABT-594 would probably be terminated. Since the results of the M99-114 trial had not yet been unblinded in March 2001, it was unclear what the development prospects for the compound were going to be until after April 2001 when the results would be unblinded and analyzed.

The Results of the M99-114 Clinical Trial and the Discontinuation of ABT-594

54. The blind on the M99-114 trial was broken on April 23, 2001. Attached hereto as D’s Exhibit DN is a true and correct copy of the Monthly Highlights for April 2001 that I prepared and circulated regarding the breaking of the blind on that date. As reflected in the Monthly Highlights, the results of the trial were not available until the week of April 30, 2001. After the results of the M99-114 trial became available, the ABT-594 development team, under my supervision, began an intensive analysis of those results that lasted several months. We had not decided as of September 2001 whether we

would continue the development of ABT-594 with a lower dose than the lowest dose that had been used during the M99-114 trial.

55. On October 5, 2001, I sent an email to several development team heads, including Dr. McCarthy, with a schedule for an upcoming PEC meeting. The PEC was created by Dr. Leiden sometime in 2001 and the committee reviewed key programs and key decisions on a monthly basis. I was in 2001 and currently am a member of the PEC. Attached hereto as D's Exhibit DF is a true and correct copy of the October 5, 2001 email I sent to Dr. McCarthy and others. As reflected in the email, ABT-594 was to be part of the discussion for the PEC meeting to be held on October 8, 2001. *Id.* at ABBT224538. On October 5, I received from Dr. Leiden an email stating that he wanted to include in the PEC meeting agenda a discussion regarding a possible additional dosing study for ABT-594. Attached hereto as D's Exhibit DG is a true and correct copy of the email I received from Dr. Leiden on October 5, 2001. During the October 8, 2001 meeting, the ABT-594 development team made a proposal for an additional dose-ranging clinical trial. After careful consideration, the PEC decided not to start a new dose-ranging trial and instead to out-license ABT-594. We concluded that although the M99-114 trial had established that ABT-594 was efficacious, the side effect profile that came with the compound would make it unattractive in the marketplace. This decision by the PEC came after months of analysis of the M99-114 results and after we had considered numerous possibilities for pursuing alternative development pathways for the compound.

#### 2001 Funding for ABT-594

56. The first Annual Research Plan for ABT-594, attached to the Agreement and provided to Hancock, disclosed that the "2001 Current Projection (Plan)" for ABT-

594 spending was “35.0” million dollars, including \$5.2 million for a Phase IIb Osteoarthritis study and \$6.3 million for Phase III studies scheduled to start in 2001.” D’s Exhibit Y at JH008121-22.

57. In late 2000, I received a copy of the Analgesia Venture 2001 Plan from the Analgesia Venture. Attached hereto as D’s Exhibit 759 is a true and correct copy of the Analgesia Venture 2001 Plan. In early 2001, I also received the Plan Final Reference Package that reflects Abbott’s planned spending in 2001 for its various compounds. Attached hereto as D’s Exhibit 616 is a true and correct copy of the March 2, 2001 Plan Final Reference Package. As reflected in both of these documents, Abbott had budgeted to spend \$9.31 million on ABT-594 through the June 2001 Go/No Go decision. D’s Exhibit 759 at ABBT144633.UR; D’s Exhibit 616 at ABBT0037544.

58. Since the M99-114 clinical trial was a critical dose-ranging trial for ABT-594, we decided to wait for the results of the trial before beginning any other clinical trials for the compound. We had scheduled a Go/No-Go decision for ABT-594 for June 2001. A Go/No Go decision is a point in the development of a compound at which determinations are made as to whether to continue or terminate the development of the compound, or to otherwise change course with the compound. The Go/No Go decision for ABT-594 in June 2001 was to be based on the data from the M99-114 clinical trial after it was unblinded in April 2001. Since the M99-114 clinical trial results would determine whether Abbott would continue to develop ABT-594, we decided to budget the ABT-594 program based on “milestone funding” through the clinical trial and “blue plan” funding of the work on the compound was planned subsequent to a Go Decision in June 2001. In Abbott’s parlance, “blue plan funding” is funding that we expect to spend

on a particular program depending on the outcome of a particular event. As reflected in the March 7-9, 2001 Portfolio Review Meeting presentation on ABT-594, we intended to spend an additional \$5.6 million on ABT-594 in 2001 after the June Go/No Go decision. D's Exhibit 620 at ABBT0048644. Provided that the decision was made to continue the development of the compound, this additional money would be spent on a Phase IIb Molar Extraction clinical study, as well as on the prepratory work necessary to initiate Phase III and additional Phase I studies at the beginning of 2002. Attached hereto as D's Exhibit 749 is a true and correct copy of a December 21, 2000 Plan Assumption Memo reflecting additional funding for ABT-594 after June 2001.

59. The change in budgeted spending on ABT-594 in 2001 that resulted from our decision to milestone fund the program until the Go/No Go decision in June 2001 was more than off-set in the budget by greater expected spending in later years and was due to the fact that the only critical path activity for the compound for much of 2001 was the M99-114 clinical trial. During the March 2001 Portfolio Review Meeting discussed above, Dr. McCarthy presented the ABT-594 development team's expected spending on the compound in 2001 and later years. As reflected in the presentation, the development team expected to spend \$59.6 in 2002 on developing the compound. D's Exhibit 620 at ABBT0048644. This amount is \$14.6 million greater than the amount disclosed to Hancock in the first Annual Research Plan for ABT-594 that was an exhibit to the Agreement. D's Exhibit Y at JH008121. The presentation also reflects that the development team expected to spend \$55.7 million in 2003, a figure that was \$23.7 million greater than the \$32 million disclosed in the Agreement. D's Exhibit Y at JH008121; D's Exhibit 620 at ABBT0048644. The projected spending for 2004 was

\$21.8, \$6.8 million greater than stated in the Agreement. D's Exhibit Y at JH008121; D's Exhibit 620 at ABBT0048644. For calendar years 2001 through 2005, we estimated spending \$163.6 million on ABT-594, an amount \$24.6 million more than the \$139 million that was disclosed in the Agreement. D's Exhibit Y at JH008121; D's Exhibit 620 at ABBT0048644.

60. The change in budgeted spending for ABT-594 in 2001 would not have delayed the development of the compound had a "Go" decision been reached in June 2001, after the unblinding of the M99-114 trial data. To the contrary, as reflected in the March 2001 Reference Package discussed above, we expected to file a New Drug Application ("NDA") in September 2003, the same date that we had disclosed to Hancock in the first Annual Research Plan for ABT-594. D's Exhibit Y at JH008121; D's Exhibit 616 at ABBT0037544. The NDA is filed with the FDA to get approval for the commercialization of a pharmaceutical compound. The Reference Package thus confirms that we did not expect the reduction in planned ABT-594 spending for 2001 to cause any delays in the schedule for the development of the compound that we had disclosed to Hancock at the time the Agreement was executed. The Reference Package also reflects that the ABT-594 Phase III trials were to be delayed only from October 2001 to April 2002 (assuming a "Go" decision after the Phase IIb trial), and that this minor delay was not expected to affect the launch date for the compound.

#### Out-Licensing of ABT-594

61. Because of the narrow therapeutic index of ABT-594 that had been shown by the unblinded Phase IIb results, the prospects for outlicensing or selling ABT-594 were very low. For example, after the Phase IIb trial, there was no interest by Purdue

Pharma, a company that had expressed interest earlier that year, in in-licensing the compound. I am aware that one potential licensee, Bayer Animal Health, expressed an interest in a potential license for ABT-594. It would have been commercially detrimental to out-license ABT-594 as a drug for animals, while Abbott was developing a compound with a similar mechanism for use in humans. Drugs that are on path to development for human use are usually not developed for animal use because of the significant commercial impact on the compound. I believe doctors generally are reluctant to prescribe their patients a drug that is being marketed for animals.

#### ABT-773

62. From 2000 through 2002, I was generally responsible for the development of ABT-773. Until April 2001, Dr. Carl Craft was the Head of the Anti-Infective Venture, which was responsible for the development of ABT-773. In or about April 2001, Dr. Stanley Bukofzer took over as Head of the Anti-Infective Venture. Both Dr. Craft and Dr. Bukofzer reported to Dr. Eugene Sun, Abbott's Division Vice-President, Global Pharmaceutical Research & Development, who in turn reported directly to me. I was kept apprised of the development of ABT-773 by Dr. Sun, as well as by Drs. Craft and Bukofzer and other members of the ABT-773 development team. From 2000 through 2002, I met and corresponded with Drs. Sun, Craft and Bukofzer, and with other members of the ABT-773 development team, to discuss the status and the ongoing clinical trials for the compound and I attended several executive-level meetings during which the status of ABT-773 was discussed. I also received the monthly status project reports created by the development team during this time period.

63. ABT-773 is a ketolide antibiotic compound that was under development by Abbott from 1997 through the summer of 2002. ABT-773 was being developed for four indications: acute bacterial exacerbation of chronic bronchitis, pharyngitis, community-acquired pneumonia, and acute bacterial or maxillary sinusitis. As reflected in the Agreement, through 2000, we had spent approximately \$188.4 million developing ABT-773. D's Exhibit Y at JH008117.

64. At the beginning of 2001, ABT-773 was one of the top four projects under development at Abbott as noted in the 2001 Reference Package. D's Exhibit 750 at ABBT0012382. It was considered the fourth most valuable compound under development by our company based on its expected value. *Id.* at ABBT0012381.

65. The final ABT-773 Descriptive Memorandum that I reviewed and that was provided to Hancock as part of the Agreement disclosed that during a Phase II trial conducted in 1999, 1% of patients taking both the 100 mg and 200 mg TID (three times a day) doses of ABT-773 experienced elevated liver function tests. D's Exhibit Y at JH008156. With regard to the dosing of ABT-773, the first Annual Research Plan for ABT-773 that was provided to Hancock as part of the Agreement disclosed that tablet dosing for ABT-773 would be "150 mg QD [once-a-day] or 150 mg BID [twice-a-day] dosing based on severity of indications." D's Exhibit Y at JH008117. With regard to the ABT-773 pediatric program, the Annual Research Plan for the compound states that the indications for ABT-773 are "Adult Tablet" and "I.V." and that disclosed that we did not plan to spend any money on pediatric or taste testing studies for the oral formulation in 2001. D's Exhibit Y at JH008117-18. The ABT-773 Descriptive Memorandum states that an "oral formulation" would "enabl[e] penetration" into the pediatric market but

makes no representations regarding the timing of the program. D's Exhibit Y at JH008153-58.

66. ABT-492, a quinolone anti-infective, was another compound included in the Hancock Agreement's basket of compounds. D's Exhibit Y at JH008179-85. The final Descriptive Memorandum for ABT-492 that I reviewed, and that was provided to Hancock as part of the Agreement, disclosed the potential for both QT prolongation and liver toxicity for the entire quinolone class of antimicrobials:

The quinolone class has potential prolongation of the QT interval and other cardiovascular effects. There is also increased regulatory scrutiny due to recent quinolone withdrawals from international markets. ABT-492 has been evaluated in the standard in vivo models used to evaluate QT interval potentials of other antibiotics and has shown no evidence of increasing QT. Also, compared to marketed quinolones, preclinical studies show no evidence or no increased incidence of . . . liver toxicity.

*Id.* at JH008184. I was not informed by anyone that Hancock was concerned about this disclosure or that it made ABT-492 less desirable to Hancock during the negotiation and finalization of the Agreement.

There Were No QT Prolongation Issues with ABT-773 as of March 2001

67. I was aware in 2000 and 2001 that it was well known that, in some circumstances, high doses of macrolide anti-infectives could have QT prolongation effects. Even though macrolides, and other types of anti-infectives, including quinolone antibiotics, are known to have the potential for such issues, anti-infectives are widely used and prescribed to patients. I was also aware during this period that the FDA was concerned generally with the potential for QT prolongation in all drugs in development, including anti-infectives. Since ketolides are a class of compounds related to macrolides, I was further aware that the FDA was paying attention to ketolides with regard to these issues and that Abbott, like other drug sponsors, would have to present data to the FDA



about ABT-773 sufficient to satisfy the Agency that the compound was safe with respect to QT prolongation.

68. I attended the End of Phase II meeting with the FDA on November 27, 2000. Attached hereto as D's Exhibit 762 is a true and correct copy of the Memorandum of Meeting Minutes that reflects my attendance at that meeting. Attached hereto as D's Exhibit 582 as a true and correct copy is also the FDA contact sheet from that meeting that I received after the meeting. My recollection is that during that meeting there was general discussion about how to demonstrate the absence of a meaningful QT prolongation signal by the FDA and that the FDA indicated that Abbott would need to show that there was no QT prolongation problem with the compound. However, the FDA did not indicate that it had seen any evidence of a QT prolongation issue with the clinical data of ABT-773. At this time, the FDA was creating guidelines for assessing potential QT prolongation effects of all drugs that were being investigated for approval.

69. On or about December 5, 2000, I attended a project review presentation for ABT-773 with Dr. Leiden. The presentation was designed to provide an overview of the ABT-773 project for Dr. Leiden. Attached hereto as D's Exhibit 787 is a true and correct copy of the December 2000 presentation for ABT-773 that I attended. As noted in the presentation, and as discussed above, we had not observed a consistent QT effect at the clinical doses of ABT-773; the effect noted in the presentation was observed during Phase I studies for doses greater than 800 mg, a dose far higher than any that would be prescribed to patients. *Id.* at ABBT205202. Based on these results, we did not believe, as of December 2000, that ABT-773 had a QT prolongation issue. The plan going

forward was to monitor QT prolongation in the Phase III along with all other routine clinical assessment studies that were being initiated.

70. On February 12, 2001, I attended a presentation to the PEC by Dr. Craft designed to update the PEC on the ABT-773 program. Attached hereto as D's Exhibit 607 are true and correct copies of the slides presented to the PEC by Dr. Craft on February 12, 2001. As reflected in the presentation, as of February 12, 2001, we had not observed a QT prolongation issue with ABT-773 at the doses at which the drug would be prescribed to patients. D's Exhibit 607 at ABBT0576844. We recognized that QT prolongation was an issue that the FDA was interested in with all classes of drugs. We therefore wanted to ensure that we met the FDA's expectations with regard to the quantity and quality of the data we collected during our clinical trials. However, since we had not seen data reflecting a QT prolongation issue with ABT-773, we did not believe it would be any more difficult for the ABT-773 program to satisfy the FDA with regard to QT prolongation that it would be for any other drug development program.

71. I attended a presentation regarding ABT-773 that Dr. Craft gave at the Portfolio Review Meeting that took place from March 7-9, 2001. Attached hereto as D's Exhibit 622 are true and correct copies of the slides presented by Dr. Craft. Dr. Craft did not present any information at that meeting that led me to believe that there was a QT prolongation issue with ABT-773. *Id.* at ABBT0013212-13. As discussed above, we were aware of the FDA's concern regarding the potential for QT prolongation issues in macrolides and ketolides as a class, but there was no evidence available to us that the compound would have clinically significant issues with QT prolongation.

72. On March 19, 2001, I attended a follow-up presentation to the PEC regarding ABT-773. Attached hereto as D's Exhibit 631 is a true and correct copy of the slides for that presentation. As noted in the presentation, there was no new information regarding the potential for QT prolongation issues in ABT-773 of which we were aware by that date. *Id.* at ABBT120480.UR.

73. In sum, during early 2001, in the period before the Hancock Agreement was executed, I was not aware of any significant unresolved issues for ABT-773 with regard to QT prolongation. While I was aware that there was a general concern at the FDA with regard to QT prolongation issues for all new drugs as well as for all anti-infectives, none of the clinical data that had been observed with regard to ABT-773 at that point raised a concern because we had not observed a QT prolongation issue at the doses we expected to prescribe to patients.

There Were No Liver Toxicity or Hepatotoxicity Issues with ABT-773 as of March 2001

74. As with QT prolongation issues, I was aware in 2000 and 2001 that the FDA was generally concerned with liver toxicity -- also known as hepatotoxicity -- with regard to many different types of drugs. With regard to ABT-773, I was also aware that in an earlier clinical trial we had observed elevated liver enzymes, biochemical markers for liver toxicity, in a few Japanese subjects who had participated in a single small Phase I study conducted as part of the Japanese ABT-773 development program. The Japanese subjects in this trial were residents of Hawaii. I was informed by the ABT-773 team that the results of this study with regard to liver toxicity were not consistent with our observations in the other clinical trials for ABT-773. The other clinical trials for ABT-773, which had included several hundred patients, had not demonstrated clinically

significant liver toxicity issues. After analysis of the results of this study we decided to repeat it, since we believed that the subjects selected for the study as well as some methodological issues skewed the results of the trial. The repeated study, which was completed in late 2000, demonstrated that the liver toxicity issues observed during the first study were not reproduced, and we concluded that the findings in the first Japanese phase I trial were not reliable and unlikely to be related to ABT-773. Attached hereto as D's Exhibit 587 is a true and correct copy of a January 2001 Monthly Project Status Report for ABT-773 that I received in January or February 2001. As reflected in the document, we had concluded in January 2001 that

*ABT-773 is clear in terms of hepatotoxicity profile* and the liver enzyme profile abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period.  
*Id.* at 0000302 (emphasis added).

75. None of the information presented in the February and March 2001 PEC updates on ABT-773 or the March Portfolio Review Presentation for ABT-773 led me to believe that ABT-773 had any hepatotoxicity issues. As reflected in those presentations, there was no evidence of liver function test increases in Japanese or Caucasian patients after the repeated Phase I study. D's Exhibit 607 at ABBT0576846; D's Exhibit 622 at ABBT0013212; D's Exhibit 631 at ABBT120481.UR.

76. As of March 2001, we did not have any clinical data that indicated there were any clinically significant liver issues with ABT-773. Nor did anyone on the ABT-773 development team inform me that they believed there were any such issues. In late 2001, the ABT-773 development team began a Phase I clinical trial to evaluate potential QT prolongation, which was referred to as the M01-325 trial. Since the FDA was, at this time, working on formal guidance for the industry regarding specific ways to measure the

potential for QT prolongation issues, we decided to put our own policy in place that would include additional trials, such as this one, specifically focused on the issue of QT prolongation. ABT-773 was one of the first drugs to be subjected to this policy. During that trial, there were unexpected liver function test elevations seen in four patients. Until that point, I had not seen any credible evidence that there was a potential liver toxicity issue with ABT-773. Attached hereto as D's Exhibit 756 is a true and correct copy of the Monthly Highlights Memorandum from November 9, 2001 that I circulated reflecting the liver function test elevations during that clinical trial.

#### The Dosing of ABT-773

77. As of March 2001, we had determined that ABT-773 would be developed for once-a-day dosing for the two less severe indications for which it was being developed, chronic bronchitis and pharyngitis. It was unclear, however, as of March 2001, whether the two more severe indications, community-acquired pneumonia ("CAP") and acute bacterial or maxillary sinusitis, would be dosed at once-a-day, commonly referred to as QD dosing, or twice-a-day, commonly referred to as BID dosing. We anticipated making the decision regarding the dosing of the two more severe indications in the summer of 2001 after we had obtained Phase III clinical trial results that would aid in the decision-making process. Attached hereto as D's Exhibit DN is a copy of the April 2001 Monthly Highlights Memorandum that I circulated reflecting that the dosing decision for ABT-773 was to be made during the summer of 2001. On July 25, 2001, a decision analysis regarding the dosing of ABT-773 was presented to Dr. Leiden and me by the ABT-773 development team. Attached as hereto as D's Exhibit DO a true and correct copy is the Monthly Highlights Memorandum from August 10, 2001 that reflects

the outcome of that meeting. Based on the information presented during the meeting, we decided to pursue BID dosing for the more severe indications, community-acquired pneumonia and acute bacterial or maxillary sinusitis. Our decision was based on the fact that we had insufficient information, as of July 2001, to determine whether QD dosing would be considered sufficient by the FDA for those indications. The choice we made was to go ahead with BID dosing for the more severe indications in order to keep the development of the compound on track. Additionally, we realized that if we were later able to satisfy the FDA that QD dosing was appropriate for the more severe indications, we could introduce such dosing post-launch, thus minimizing any potential negative commercial impact that might result from an initial BID launch for the more severe indications.

#### The Pediatric Program

78. We always intended to develop a pediatric formulation for ABT-773, if possible, and the ABT-773 program had a plan to accomplish that goal from 2000 on. As noted in the December 2000 presentation on ABT-773 that I attended, we initiated the pediatric program for ABT-773 in January 2000. D's Exhibit 787 at ABBT205238. In September 2000, the ABT-773 development team conducted its first taste evaluations of the oral formulation of the compound intended for pediatric use and found that it had a bitter taste that would place it at a competitive disadvantage; it therefore needed to be reformulated. As set forth in the December 2000 presentation, the ABT-773 team had developed a pediatric program plan that contemplated the development of a new pediatric formulation with a Go/No Go decision in June 2001, and which also contemplated clinical testing of that pediatric formulation. Since the ABT-773 team was principally

focused on the tablet formulation, we decided to delay the development of the pediatric formulation until the tablet formulation Phase III clinical trials were underway.

79. Pharmaceutical companies usually develop and study the pediatric patient populations with a new drug only after the corresponding adult program has acquired a significant amount of adult data. It is generally judged unacceptable to expose children to products without having demonstrated substantial activity and especially safety in adults first. The FDA's Pediatric Rule did not require that we develop a pediatric formulation for ABT-773 before the adult tablet could be launched. The Pediatric Rule only required Abbott to initiate pediatric work at some time prior to the regulatory approval of the adult formulation. Moreover, the Pediatric Rule also contemplates that a drug sponsor can obtain a waiver or a deferral of the requirements of the rule under certain circumstances.

80. On September 18, 2001, I sent an email to Dr. Bukofzer and Ms. Meyer asking about the status of the pediatric program for ABT-773. Attached hereto as D's Exhibit AL is a true and correct copy of my September 18, 2001 email and Dr. Bukofzer's responses to the questions posed in that email. As noted in Dr. Bukofzer's response, work on a new formulation for the pediatric program was expected to begin in October 2001 and the first clinical trial for the new formulation was expected to start six months later. *Id.* at ABBT203480. In fact, formulation work for the Pediatric Program began in October 2001. Attached hereto as D's Exhibit DH is a true and correct copy of the October 8, 2001 Monthly Highlights Memorandum that I prepared reflecting that additional formulation work was being undertaken in October 2001.

81. During 2000 and 2001, I did not believe that the FDA's Pediatric Rule would pose an obstacle to our ability to obtain regulatory approval from the FDA to launch ABT-773. Nor did I believe that the requirements of the rule would delay that launch. I believed that the work we had done and intended to do on the ABT-773 pediatric program would be sufficient to satisfy the FDA that we had met the requirements of the rule, or that we could obtain a waiver or deferral of those requirements.

The April 2001 Ketek Advisory

82. In April 2001, the Anti-Infective Drugs Advisory Committee for the FDA held its first Advisory Committee meeting for Ketek, a ketolide that was under development by Aventis, another pharmaceutical company. An FDA advisory committee is a group of outside experts who provide advice to the FDA regarding specific areas under the purview of the FDA. The opinions expressed by the FDA's advisory committees carry significant weight in the FDA's determination of whether a drug is approved or not, and frequently the Advisory Committee's deliberations will determine the nature of additional clinical investigation before or after approval is granted.

83. As of early 2001, Ketek was at a more advanced stage of development than any other ketolide. We had expected that the Advisory Committee would be focused principally on efficacy concerns since there were so many efficacious anti-infectives already on the market. In fact, however, the Advisory Committee focused very heavily on the size of Ketek's safety database for both QT prolongation and liver toxicity. We had expected to run a number of Phase III and additional Phase I trials for ABT-773, with the understanding that we would need to demonstrate that ABT-773 was clear of QT



prolongation and liver toxicity issues. Based on only a small number of incidents of elevated liver function tests in the Ketek clinical trials, the FDA was requiring additional clinical trials that included over 20,000 patients. Based on the four incidents of elevated liver function tests that we observed in the October 2001 Phase I trial, we were concerned that we would also be required to conduct additional clinical trials that would include 20,000 patients as well.

84. The Advisory Committee meeting demonstrated to us that the safety hurdle for anti-infectives, and with that ketolide anti-infectives, had increased well beyond our original understanding. The evolving standard to demonstrate the absence of an issue in far larger numbers of patients than what was traditionally the case for anti-infective programs meant that the expense and likely duration of developing the compound as well as adequately demonstrating its safety would be substantially increased. Based on the Ketek advisory, we realized that the expected value of ABT-773 had fallen dramatically. The Ketek advisory revealed that Aventis would be required to perform a greater than 20,000 patient study to determine the incidence of liver toxicity because of only two specific cases of liver toxicity that had occurred in the Ketek database. This information was significant because up until that time our experience was that a very low incidence of liver toxicity in a clinical trial did not affect the FDA's recommended safety database so greatly. As noted above, in October 2001, we had observed convincing evidence of elevated liver function tests in one of our ABT-773 studies in October 2001. We realized that the newly expanded study was expected to cost Aventis over \$100 million and last several years, a cost that we had not accounted for in the development of ABT-773. In sum, the information we received after the Ketek

advisory made it clear that the cost of developing ABT-773 had increased substantially from what we had initially planned.

The Discontinuation of ABT-773

85. In late 2001, I attended a PEC up-date presentation regarding ABT-773 that was given by Dr. Bukofzer. Attached hereto as D's Exhibit 760 is a true and correct copy of the Summary of the December 1, 2001 PEC meeting that I received after that meeting. Also attached as D's Exhibit EC is a true and correct copy of the presentation given by Dr. Bukofzer at that meeting based on the ABT-773 clinical data that had been acquired and analyzed by late 2001. Based on the results and implications of the Ketek Advisory Committee's findings, the PEC made the decision not to start any new ABT-773 activities or studies, but to continue all ongoing activities and studies.

86. On January 9, 2002, I attended a meeting with Mr. Miles White, Abbott's Chief Executive Officer and Chairman of the Board, regarding ABT-773. Attached hereto as D's Exhibit DQ is a true and correct copy of the meeting notice for that meeting. Prior to that meeting, Dr. Bukofzer and Dr. Sun drafted and circulated a Memorandum, dated January 22, 2002, concerning the development status of ABT-773. Attached hereto as D's Exhibit 761 is a true and correct copy of that Memorandum, which I received on or around January 17, 2002. I believe that Dr. Bukofzer, Dr. Sun, Dr. Leiden and Mr. Arthur Higgins also attended this meeting with Mr. White. At this meeting, we discussed generally the fact that information had been developed since April 2001 that indicated that ABT-773 had significantly deviated from its target product profile. I believe the January 2002 Memorandum accurately reflects the details of what was discussed during that meeting.

87. At the end of 2001 and the beginning of 2002, we found ourselves increasingly in the position of trying to prove a negative with regard to ABT-773. While we did not believe that ABT-773 had any specific QT prolongation or liver issues that were worse than other anti-infectives that had been approved by the FDA and that had already been marketed successfully, the Ketek advisory in April demonstrated to us that the FDA would require substantial additional work and patients than we had originally forecast for the program. At that time we realized that the program could be far longer and much more expensive than we had originally intended it to be.

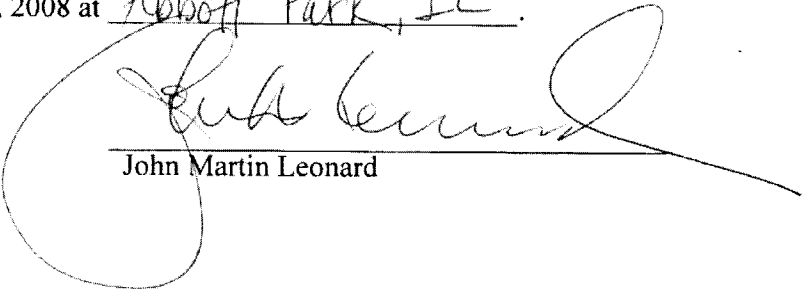
88. Work on ABT-773 projects that had been initiated prior to the PEC meeting continued through the beginning of 2002. Attached hereto as D's Exhibit DR is a true and correct copy of the February 8, 2002 Monthly Highlights Memorandum that I circulated that reflects that the Phase I QT study amendment had been approved and that the study was scheduled to re-start by the end of February 2002. Additionally, two ongoing studies were enrolling additional patients during January 2002. A Phase I study was re-started in March 2002 and there was one additional study that was ongoing in March 2002. Attached hereto as D's Exhibit DS hereto is a true and correct copy of the April 9, 2002 Monthly Highlights Memorandum I circulated reflecting the ongoing activities for ABT-773.

89. Eventually, in the summer of 2002, after careful consideration, the PEC made the decision to discontinue the development of ABT-773 and to out-license the compound based on the new information discussed above regarding challenges to the development of ABT-773 that had become available after April 2001, including the clinical data accumulated since that date that indicated that ABT-773 was deviating

significantly from its target profile and the information learned as a result of the Ketek advisory.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 2/15, 2008 at Abbott Park, IL.



John Martin Leonard

**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

\_\_\_\_\_  
/s/ Eric J. Lorenzini

Eric J. Lorenzini (*pro hac vice*)

**A**

2:30 -  
3:30  
Juv  
available

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ABBT 0006627



To:

ATTACHED ARE OUR DILIGENCE  
+ 'RESEARCH' PLAN DOCUMENTS  
FOR JOHN HANCOCK. PLEASE  
REVIEW TO INSURE WE'RE  
DISCLOSING 'MATERIAL INFO.'  
TRYING TO SEND THEM OUT  
ON MONDAY.

From:  
STEVE COHEN  
Controller  
PPD R&D  
D-404. AP9  
Ext. 7-3418

*Steve*  
Overall, I have little to  
add. I don't know who prepared  
the descriptive memorandum, but  
they appear to be well written and  
probably what Hancock is  
looking for.



*Sh*

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ABBT 0006628

**Pharmaceutical Products Division**  
**Sample Direct/Indirect Rate & Headcount Distribution**  
**2001 Plan**

<u>Rate:</u>	<u>Data Management</u>	<u>Toxicology/Pathology</u>
<b>Direct</b>		
Payroll (Both PMP and Supv/Mgr)	6,577	5,277
Office Supplies	53	51
T & E	26	84
Sem/Edu	21	73
Supplies	41	440
Consultant	291	67
Printing	73	4
Clinical Tracking Costs	4,075	...
Depreciation	1,031	258
UNIX Based Support	3,453	921
Utilities	62	...
Floorspace	579	1,479
Housekeeping	23	...
Other	112	389
<b>Sub-Total Direct</b>	<b>16,416</b>	<b>9,042</b>
<b>Indirect</b>		
Patents & Trademarks	285	388
Corporate Indirect	697	949
PPD Indirect (Mgmt.)	337	458
Department Overhead	396	584
Other	46	62
<b>Sub-Total Indirect</b>	<b>1,761</b>	<b>2,441</b>
<b>Total</b>	<b>18,177</b>	<b>11,483</b>
<b>% Direct</b>	<b>90%</b>	<b>79%</b>
<b>% Indirect</b>	<b>10%</b>	<b>21%</b>
<b><u>Headcount:</u></b>		
<b>Direct Headcount</b>	<b>123</b>	<b>53</b>
<b>Indirect Headcount</b>	<b>17</b>	<b>7</b>
<b>Total Headcount</b>	<b>140</b>	<b>60</b>
<b>Rate</b>	<b>92.06</b>	<b>135.42</b>
<b>Hours</b>	<b>1,600</b>	<b>1,600</b>
<b>Annual Rate</b>	<b>147,296</b>	<b>216,672</b>

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ABBT 0006629

**Pharmaceutical Products Division  
Sample Direct/Indirect Project Funding Distribution  
2001 Plan (\$000)**

	ABT - 773 (Late Stage - Phase III)			MMPI (Early Stage)		
	Direct	Indirect	Total	Direct	Indirect	Total
PPD Investigational Drug	0.3	0.0	0.4	-	-	-
Venture Management	4.8	1.6	6.5	0.8	0.2	0.9
Discovery	2.2	0.2	2.4	1.1	0.3	1.3
Drug Safety	1.6	0.2	1.7	1.8	0.3	2.1
PARC	4.8	0.4	5.3	0.8	0.2	1.0
Phase I Center	2.0	0.1	2.1	0.1	0.0	0.1
Development Operations	4.2	0.5	4.6	0.1	0.0	0.1
Regulatory Affairs	0.2	0.0	0.3	0.0	0.0	0.0
Medical Affairs	0.8	0.1	0.9	0.0	0.0	0.0
Administration	1.6	-	1.6	0.1	-	0.1
AI Manpower	0.7	-	0.7	-	-	-
Bulk Drug / Process	15.0	-	15.0	-	-	-
Clinical Grants	43.1	-	43.1	1.3	-	1.3
<b>Total</b>	<b>81.4</b>	<b>3.2</b>	<b>84.6</b>	<b>6.2</b>	<b>0.9</b>	<b>7.1</b>
<b>% Split</b>	<b>96.2%</b>	<b>3.8%</b>	<b>100.0%</b>	<b>86.6%</b>	<b>13.4%</b>	<b>100.0%</b>

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ABBT 0006630

2001 KEY RATES									
	2000			2001			% Change		
	Rate	Hours	Annual Rate	Rate	Hours	Annual Rate	Hourly Rate	Total Hours	Annual Rate
<u>DRUG SAFETY</u>									
Toxicology/Pathology - PMP/TMP	121.52	1,680	204,154	135.42	1,600	216,672	11.4%	-4.8%	6.1%
Metabolism/Microscopy - PMP/TMP	144.75	1,600	231,600	141.64	1,650	233,706	-2.1%	3.1%	0.9%
Comparative Medicine - PMP/TMP	115.60	1,768	204,381	116.88	1,850	216,228	1.1%	4.6%	5.8%
Strategic & Exploratory - PMP/TMP	121.52	1,680	204,154	173.56	1,600	277,696	42.8%	-4.8%	36.0%
<u>PHASE I CENTER</u>									
Pharmacokinetics 4PK -PMP/TMP	144.75	1,600	231,600	135.00	1,600	216,000	-6.7%	...	-6.7%
Clin. Res. MDs 42P - PMP	...	...	...	180.35	1,500	270,525	...	...	...
Clin Res. Spec. 420-PMP/TMP	113.59	1,700	193,103	123.75	1,700	210,375	8.9%	...	8.9%
<u>PARD</u>									
Prod Dev - PMP, TMP	108.54	1,800	195,372	116.71	1,800	210,078	7.5%	...	7.5%
IDS - PMP, TMP	160.80	1,600	257,280	162.11	1,600	259,376	0.8%	...	0.8%
<u>DEV OPERATIONS</u>									
Data Mgmt D433 - TMP/PMP	90.04	1,600	144,064	92.06	1,600	147,296	2.2%	...	2.2%
Stats - PMP/TMP	97.75	1,800	175,950	99.10	1,800	178,380	1.4%	...	1.4%
<u>RA/QA</u>									
RA/QA - PMP & TMP	125.50	1,600	200,800	134.49	1,600	215,184	7.2%	...	7.2%
<u>DISCOVERY</u>									
	137.65	1,800	247,770	142.91	1,800	257,238	3.8%	...	3.8%

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ABBT 0006631

**Endothelin (ABT-627)  
Development Statistics**

Therapeutic Area	Oncology				
Indications	<ul style="list-style-type: none"> <li>- Hormone Refractory Prostate Cancer</li> <li>- Potential for use in early Prostate Cancer and other cancer types</li> </ul>				
Description	<ul style="list-style-type: none"> <li>- ABT-627 is Abbott's leading endothelin antagonist receptor</li> <li>- ABT-627 is seeking an indication for the treatment of hormone refractory prostate cancer</li> <li>- ABT-627 will probably be used with current therapies</li> <li>- Well tolerated as chronic therapy</li> <li>- Oral administration</li> <li>- No major drug interactions with drugs commonly used in elderly population or hormonal therapy</li> <li>- Demonstrated cost effectiveness at filing</li> </ul>				
Current Time Line	Milestone	Date			Spending
	Phase I Phase II Phase III NDA Filing Launch	2Q1996 4Q1997 4Q2000 2Q2004 4Q2004			
					Project-to-Date-Spending (thru '00) 2001 Current Projection (Plan) * See page 2 for detail.
					127.6 38.0*
Projected Spending by Year					
	2000	2001	2002	2003	2004
PC*	13.0	38.0	40.0	33.0	20.0
EPcA*	N/A	6.0	6.0	5.0	0.0
FE*	N/A	5.0	3.0	0.0	0.0
					Total
					154.0 17.0 8.0
* End of Phase II meeting with FDA just completed. Budget impact still in process plus discussion of other cancer indications ongoing. 2001 range \$35-40 depending on outcome of discussion.					

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ABBT 0006632



**Ketolide Oral & IV (ABT-773)  
Development Statistics**

Therapeutic Area	Antibacterial									
Indications	Adult Tablet: Community-acquired respiratory infections. I.V.: Step-down therapy in community-acquired hospitalized pneumonia.									
Description	<ul style="list-style-type: none"><li>- ABT-773 is a potent ketolide with strong activity against most macrolide resistant strains, while maintaining the broad spectrum coverage of clarithromycin.</li><li>- Product will be available as tablet and IV formulation.</li><li>- ABT-773 will address the major unmet medical needs of increasing resistance to current empiric agents, particularly S. pneumoniae.</li><li>- Maintains clari's claim of "Spans the spectrum" (G+, G-, atypicals).</li><li>- Cover key G+ resistant strains (S. pneumoniae, S. pyogenes).</li><li>- Tablet dosing is 150mg QD or 150mg BID dosing based on severity of indications.</li><li>- Tablet: 5 days for ABECB, pharyngitis, 10 days for AMS and CAP.</li><li>- Incidence of GI side effects equal to clari (assuming comparable drug levels to tablet).</li><li>- COGS target \$2,500/kg at launch for tablet.</li></ul>									
	Current Time Line	Milestone	Tablet Date	IV Date	Spending					
		Phase I	1Q1997	1Q2001	<div>Project-to-Date-Spending (thru '00) 2001 Current Projection (Plan) * See page 2 for detail.</div>					
		Phase IIb	3Q1999	N/A						
		Phase III	4Q2000	4Q2001						
	NDA Filing	3Q2002	2Q2003							
	Launch	1Q2004	2Q2004							
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total			
	74.1	91.5	69.0	45.0	32.0	22.0	333.6			

**Ketolide (ABT-773)**  
**2001 Plan Development Cost Summary**

Program Status		1999				2000				2001				2002				2003				2004			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase IIb (Tablet)																									
Phase III (Tablet)																									
<div>Tablet NDA Filing</div> <div>Tablet Launch</div>																									
Major Development Activities and Costs																									
Clinical Program		Total Patients	Enrolled 9/29/00	Start	End	2000 AGU Cost	2001 Plan Cost																		
		Phase IIB Studies (3 indications)	863	Sep-99	Jun-00	\$5,017	\$0																		
		Phase III (4 Indications)	5,440	Nov-00	May-02	\$10,885	\$41,051																		
		Japan Studies	TBD	Oct-00	Dec-01	\$1,723	\$4,000																		
		Pediatric PK/PPD / Taste Testing Studies	24	Mar-00	Sep-00	\$575	\$0																		
		External Special Population Studies	36	Mar-00	Mar-01	\$1,686	\$63																		
		Internal Bio Studies (Phase I Center)	250	Jan-01	Dec-01	\$2,524	\$2,150																		
		Microbiology Grants	N/A	Jan-01	Dec-01	\$2,000	\$2,000																		
		Venture Management				\$5,436	\$6,863																		
		European Venture Research				\$1,133	\$1,474																		
Data Management/Statistics				\$3,519	\$5,037																				
						<u>\$34,498</u>	<u>\$62,638</u>																		
Chemistry, Manufacturing, and Controls (CMC)																									
Formulation & Analytical Bulk Drug / Process	2000 AGU						2001 Plan																		
	\$6,676						\$5,594																		
	\$24,529						\$16,432																		
						<u>\$31,205</u>	<u>\$22,026</u>																		
Drug Safety Support	2000 AGU						2001 Plan																		
	\$3,374						\$1,749																		
	<u>\$3,374</u>						<u>\$1,749</u>																		
Other Support Costs	2000 AGU						2001 Plan																		
	\$2,886						\$2,418																		
	\$1,361						\$891																		
	\$679						\$887																		
	\$97						\$891																		
						<u>\$91,500</u>																			

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ABBT 0006635



**CCM (ABT-594)  
Development Statistics**

Therapeutic Area	Neuroscience																														
Indications	ABT-594 primary target indication is the treatment of neuropathic pain (NP).																														
Description	<ul style="list-style-type: none"><li>- ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator.</li><li>- ABT-594 is effective in nociceptive pain and neuropathic pain.</li><li>- ABT-594 is expected to have a better side effect profile than opioids, no tolerance, no abuse, and no DEA scheduling.</li><li>- Pre clinical data show ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in treating moderate to severe pain in several well characterized animal models of pain.</li><li>- ABT-594 has a unique mechanism of action which may enable use in combination with other analgesics as well as monotherapy.</li><li>- Slow onset of action (approx. 1.5 - 3 hours) at low doses tested may suggest limited utility in acute pain types.</li><li>- Favorable safety profile.</li><li>- Oral formulation, BID dosing.</li></ul>																														
Current Time Line	<table><tr><th>Milestones</th><th>Date</th></tr><tr><td>IND Filing</td><td>4Q1998</td></tr><tr><td>Phase I</td><td>3Q1997</td></tr><tr><td>Phase II</td><td>3Q1998</td></tr><tr><td>Phase III</td><td>4Q2001</td></tr><tr><td>NDA Filing</td><td>3Q2003</td></tr><tr><td>Launch</td><td>3Q2004</td></tr></table>		Milestones	Date	IND Filing	4Q1998	Phase I	3Q1997	Phase II	3Q1998	Phase III	4Q2001	NDA Filing	3Q2003	Launch	3Q2004	<table><tr><th colspan="2">Spending</th></tr><tr><th></th><th>\$</th></tr><tr><td>Project-to-Date Spending (thru '00)</td><td>97.3</td></tr><tr><td>2001 Current Projection (Plan)</td><td>35.0*</td></tr></table>					Spending			\$	Project-to-Date Spending (thru '00)	97.3	2001 Current Projection (Plan)	35.0*	* See page 2 for detail.	
Milestones	Date																														
IND Filing	4Q1998																														
Phase I	3Q1997																														
Phase II	3Q1998																														
Phase III	4Q2001																														
NDA Filing	3Q2003																														
Launch	3Q2004																														
Spending																															
	\$																														
Project-to-Date Spending (thru '00)	97.3																														
2001 Current Projection (Plan)	35.0*																														
Projected Spending by Year	<table><tr><th></th><th>2000</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>Total</th></tr><tr><td></td><td>14.4</td><td>35.0</td><td>45.0</td><td>32.0</td><td>15.0</td><td>12.0</td><td>153.4</td></tr></table>								2000	2001	2002	2003	2004	2005	Total		14.4	35.0	45.0	32.0	15.0	12.0	153.4								
	2000	2001	2002	2003	2004	2005	Total																								
	14.4	35.0	45.0	32.0	15.0	12.0	153.4																								

**ABT-594**  
**2001 Plan Development Cost Summary**

Program Status	1997				1998				1999				2000				2001				2002				2003				2004			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																

**Quinolone ABT-492  
Development Statistics**

Therapeutic Area		Anti-bacterial	
Indications		<ul style="list-style-type: none"> <li>Community acquired respiratory, nosocomial pneumonia, complicated and uncomplicated urinary tract and skin/soft tissue infections.</li> <li>ABT-492 is a potent broad-spectrum quinolone with activity against Gram+, Gram-, and atypical pathogens, including most penicillin, macrolide, and quinolone resistant strains of S. pneumo.</li> <li>Commercial objective is "Trovan-like" activity with "Levaquin-like" safety.</li> <li>Preliminary in-vitro safety assays suggest good safety profile.</li> <li>Product will be available in tablet and injectable formulations.</li> <li>Targeting QD dosing for both formulations (not confirmed).</li> <li>Targeting 5-7 day dosing for most indications (not confirmed).</li> <li>COGS at \$1,500-3,200/kg at launch pending chemistry optimization.</li> </ul>	
Description			
Current Time Line	Milestone	Date	Spending
	Phase I Phase II Phase III NDA Filing Launch	4Q2000 3Q2001 3Q2002 4Q2004 4Q2005	<div> <div>Project-to-Date-Spending (thru '00)</div> <div>2001 Current Projection (Plan)</div> <div>* See page 2 for detail.</div> </div> <div> <div>\$</div> <div>46.3</div> <div>25.0*</div> </div>
Projected Spending by Year		<div> <div>2000</div> <div>6.8</div> </div> <div> <div>2001</div> <div>25.0</div> </div> <div> <div>2002</div> <div>75.0</div> </div> <div> <div>2003</div> <div>100.0</div> </div> <div> <div>2004</div> <div>52.0</div> </div> <div> <div>2005</div> <div>11.0</div> </div> <div> <div>Total</div> <div>269.8</div> </div>	

**Quinolone (ABT-492)**  
**2001 Plan Development Cost Summary**

Program Status		Timeline																				Launch																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																							
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**TSP (ABT-510)**  
**Development Statistics**

Therapeutic Area		Oncology					
Indications		Solid tumors such as lung, breast, ovary, bladder and pancreas.					
Description		<ul style="list-style-type: none"><li>- Thrombospondin peptide</li><li>- Novel anti-angiogenesis agent</li><li>- Parenteral dosing</li><li>- ABT-510 is seeking an indication for the treatment of solid tumors</li><li>- Mechanism may prevent the growth of tumors and prevent the spread of metastases by preventing or inhibiting the growth of nutrient supplying blood vessels</li></ul>					
Current Time Line	Milestone	Date	Spending				
	DDC	4Q1998	\$				
	Phase I	4Q2000	Project-to-Date-Spending (thru '00)				
	Phase II	3Q2001					
	Phase III	1Q2003	2001 Current Projection (Plan)				
	NDA Filing	1Q2005					
	Launch	1Q2006	* See page 2 for detail.				
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
	6.6	9.0	37.0	29.0	23.0	15.0	119.6

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ABBT 0006640



**FTI (ABT-xxx)**  
**Development Statistics**

Therapeutic Area		Oncology								
Indications		Solid tumors such as lung, breast, ovary, bladder and pancreas.								
Description		<ul style="list-style-type: none"><li>- Farnesyltransferase Inhibitor.</li><li>- Mechanism of action is unknown, but thought to inhibit farnesylated proteins which are integral for malignant tumor growth.</li></ul>								
		Current Time Line					Spending		\$\$	
		Milestones	Date				Project-to-Date-Spending (thru '00)		35.0	
		DDC	1Q/2001				2001 Current Projection (Plan)		6.0*	
		Phase I	4Q/2001				* See page 2 for detail.			
		Phase II	2Q/2003							
		Phase III	3Q/2004							
		NDA Filing	4Q/2006							
		Launch	4Q/2007							
Projected Spending by Year		2000	2001	2002	2003	2004	2005	Total		
		N/A	6.0	15.0	30.0	30.0	18.0	99.0		

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ABBT 0006642





**MMPI (ABT-518)**  
**Development Statistics**

Therapeutic Area		Oncology	
Indications		Solid tumors such as lung, ovarian, pancreas, breast, colorectal and bladder.	
Description		<ul style="list-style-type: none"> <li>- Novel metalloproteinase inhibitor.</li> <li>- Cytostatic mechanism.</li> <li>- Oral dosing.</li> <li>- May prevent the growth of metastatic lesions and/or inhibit primary tumor growth.</li> <li>- Superior efficacy or side-effect profile to competitive agents.</li> </ul>	
Current Time Line	Milestone	Date	Spending
	DDC Phase I Phase II Phase III NDA Filing Launch	1Q2000 4Q2000 2Q2002 3Q2003 3Q2005 3Q2006	<div>Project-to-Date Spending (thru '00)</div> <div>2001 Current Projection (Plan)</div> <div>* See page 2 for detail.</div> <div> <div>\$</div> <div>40.0</div> <div>7.0*</div> </div>
Projected Spending by Year		<div>2000</div> <div>5.0</div> <div>2001</div> <div>7.0</div> <div>2002</div> <div>31.0</div> <div>2003</div> <div>35.0</div> <div>2004</div> <div>26.0</div> <div>2005</div> <div>20.0</div> <div>Total</div> <div>124.0</div>	

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**MMPI (ABT-518)**  
**2001 Plan Development Cost Summary**

Program Status	1999				2000				2001				2002				2003				2004				2005				2006			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																
NDA																																
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**Anti-Mitotic (ABT-751)  
Development Statistics**

Therapeutic Area		Oncology						
Indications		Solid tumors such as breast, lung, colorectal, and ovarian						
Description		<div>- Novel oral cytotoxic agent that inhibits tumor growth by inhibiting the polymerization of tubulin, similar to the MOA of taxanes</div> <div>- May be effective in patients resistant to other cytotoxic agents</div>						
Current Time Line	Milestone	Date						Spending
	In-LICENSE	2Q2000						\$
	Phase I	1Q/2001						Project-to-Date-Spending (thru '00)
	Phase II	4Q/2001						41.0
	Phase III	4Q/2002						2001 Current Projection (PLAN)
	NDA Filing	1Q/2005						10.0*
	Launch	1Q/2006						* See page 2 for detail.
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total	
	6.0	10.0	27.0	35.0	25.0	12.0	115.0	

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ABBT 0006646

## Anti-Mitotic (ABT-751) 2001 Plan Development Cost Summary

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**CONFIDENTIAL**

**ABT – 773**

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**

Nov. 1, 2000

Hancock – ABT-773

**CONFIDENTIAL**

ABBT 0006648

**ABT-773***Opportunity Overview*

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase IIb trials. It is scheduled to begin in phase III clinical trials in Q4, 2000 and has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

*The US Market*

The overall antibiotic market in the U.S. reached \$8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceflin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
<b>TOTAL TAB/CAP</b>	<b>\$5,715.4</b>	<b>100.0%</b>	<b>8.9%</b>	<b>221.5</b>	<b>100.0%</b>	<b>0.1%</b>

*U.S. Market Projections*

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everminomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

*The Ex-U.S. Market*

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

*Scientific Rationale for ABT-773*

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant gram + organisms, particularly macrolide resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

*Clinical Studies*

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Presumed Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	6% (3/48)

Clinical and Bacteriological Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

*Patent Status*

ABT-773 will have patent exclusivity through 2016.



- **Appendix 1**

**Key Emerging Competitors**

<b>Generic</b>	<b>Brand</b>	<b>Company</b>	<b>Class</b>	<b>Status</b>
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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**ABT – 510**

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**

November 1<sup>st</sup>, 2000

Hancock\_ABT 510

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ABBT 0006653

**ABT 510***Overview*

There is abundant evidence that primary tumor growth and metastatic progression require new blood vessel formation (angiogenesis). Tumors secrete inducer proteins including bFGF and VEGF that activate microvascular endothelial cells (EC) causing them to proliferate, migrate and organize into capillary structures. Activated endothelial cells also enhance malignant progression by producing signal molecules (cytokines) that inhibit programmed cell death (apoptosis) of tumor cells. Since anti-angiogenic therapy targets genetically stable endothelial cells, resistance typically seen following cytotoxic chemotherapy is not observed. Moreover, angiogenesis inhibitors should not have the intrinsic toxicity of anti-proliferative chemotherapy. Angiogenesis is also a feature of several other pathophysiologic states of large unmet medical need (macular degeneration, psoriasis, and arthritis, among others).

Angiogenesis sustains the growth and progression of tumors. Unlike chemotherapy or radiation, both of which can damage normal cells in addition to tumor cells, anti-angiogenic agents are hypothesized to prevent growth of new blood vessels and to disrupt critical tumor survival signals produced by EC. These agents may keep tumors in a dormant state for as long as the compound is administered and tumor regressions may occur. Proof of this principle has been demonstrated in pre-clinical models. Currently, at least thirteen compounds with anti-angiogenic activity in cancer are in various phases of clinical development, however few act directly and specifically on the angiogenesis process. Anti-angiogenesis drugs are not expected to replace or compete with current therapies. Instead, if these agents prove to be effective, it is believed that they will be used as supplemental therapy to prevent metastasis following surgery, cytotoxic chemotherapy or radiotherapy. As for cases where tumors have already metastasized, these agents could slow down disease progression and maintain "disease dormancy".

Thrombospondin-1 (TSP-1) was the first natural angiogenesis inhibitor to be discovered. TSP-1 is a large, multifunctional protein. TSP-1 rapidly inhibits EC migration and increases EC apoptosis through activation of caspase-3-like proteases. The normal tissue expression of TSP-1 limits inappropriate neovascularization, however it is transcriptionally activated by the tumor suppressor gene product p53. Therefore, TSP-1 is down-regulated and under-produced in p53 defective tumors. In rodent models, ectopic overexpression of TSP-1 inhibits the malignant phenotype as does direct administration of TSP-1 in the circulation. However, direct clinical use of TSP-1 is not feasible because of its scarcity, large size and multiple other biological functions.

The angiogenic activity of TSP-1 has been localized to the 50,000 MW N-terminal stalk region of this protein, and more specifically to the properdin (Type-1) repeats within this region. Although small synthetic peptides within this region have only weak antiangiogenic activity, it was discovered that a single D-amino acid replacement in a properdin region peptide led to an increase in activity of greater than 1000-fold. ABT-510 is a parenterally available nonapeptide. Although ABT-510 competes with TSP-1 for binding to the EC, the exact mechanism of anti-angiogenesis is unknown.

ABT 510 is supplied for clinical use as a sterile solution in acetate salt in 5% dextrose. ABT 510 is soluble and stable in water.

In vitro, ABT 510 inhibits chemotactic VEGF/bFGF-stimulated migration of human microvascular endothelial cells (EC) with an IC<sub>50</sub> of approximately 0.250 nM. This effect is EC specific. ABT-510 (10mg/kg/day subcutaneously) blocks VEGF-induced corneal vascularization in mice. It potently and selectively competes with TSP-1, binding the CD 36 receptor.

ABT 510 inhibits tumor progression in vivo. ABT 510(20mg/kg/day subcutaneous administration) inhibited tumor progression (78% growth inhibition at day 38) in a model of human breast cancer (MDA-MB-435) growing in the breast pads of nude mice. Dose dependent inhibition of B16F10 melanoma lung metastases was observed in a second murine model.

Assays for toxicity, histamine release, hemolysis, T-cell function neutrophil migration, platelet aggregation, receptor (CEREP) screening and CNS function were unremarkable. ABT-510 produced no physiologically significant changes in cardiovascular or hemodynamic function in anesthetized dogs. In addition, there were no physiologically significant changes in clinical blood chemistry profiles or cardiac electrophysiologic function in response to ABT-510. Doses that were many times higher than the predicted efficacious concentration produced a moderate reduction in mean arterial blood pressure in conscious monkeys. ABT-510 was not mutagenic in the Ames assay. It is concluded therefore that ABT-510 has an excellent pre-clinical safety profile.

ABT-510 is currently in Phase I clinical trials. Because of its exceptional safety profile, normal volunteers are being dosed with ABT-510 to establish human safety and pharmacokinetic parameters. Review of these data will lead to a Go/NoGo decision for Phase II trials in the Summer of 2001.

#### *The market*

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market. The market for products to treat cancer is changing rapidly. It is a growing market fueled by:

- Increasing disease incidence
- New product entries
- New therapeutic paradigms
- A growing adjunctive market, which increases the number of patients eligible for chemotherapy
- Intense research and competition

The increase in the aging population in developed countries increases the incidence of cancer. The diagnosed cancer incidence and prevalence in seven major markets, including the U.S., France, Germany, Italy, Spain, U.K. and Japan are close to 3 million and 10 million respectively. The numbers are increasing steadily. Currently, about one-third of the new medicines in development are targeted against cancer.

Cancer is not a single disease, but includes more than 100 different disorders, which have at their core uncontrolled cell growth. Of these disorders, the cancer types that offer the greatest commercial opportunity include breast, colorectal, lung, ovarian and prostate (based on incidence/prevalence/unmet need). Treatment of breast, lung and prostate cancers account for more than 50 percent of the direct medical costs of cancer therapies. Other cancer types, specific to one or more of the major international markets, may provide niche opportunities. For instance, stomach (gastric) cancer is relatively common in Japan but not in the U.S. or Europe; similarly, liver cancer has a greater occurrence in Japan, Italy and Spain.

Depending on tumor type, cancer can be treated with surgery, radiation, chemotherapy (cytotoxic), hormonal therapy or a combination of any of these. For the purpose of this analysis, we will define the cancer market as chemotherapeutics and the adjunctive therapies used to counter the effects of chemotherapy and radiation therapy. The following charts summarize the global sales for these products.

**Global Sales by Market Segment (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
Hormone	4,414	4,784	4,884	5.2%
Cytotoxic	4,278	5,212	6,268	21.0%
Adjunctive	3,367	3,651	4,166	11.2%
Total	12,059	13,647	15,318	12.7%

Source: Datamonitor

**Sales by Region (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
US	5,564	6,276	7,422	15.5%
Ex- US	6,495	7,370	7,896	10.3%

Source: Datamonitor

*Chemotherapeutic agents*

*Cytotoxic therapies* include classes such as alkylating agents, anti-tumor antibiotics, anti-metabolites and antimitotics (taxanes). These agents are toxic and demonstrate dose-limiting side effects. The commercial value of this segment is significantly understated, as most of the products are available in generic form.

The growth of the cytotoxic segment in the past three years has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Utilization of these newer agents, however, appears to be dependent on the cost sensitivity of the local market. For example, secondary sources indicate that Taxol has recorded over 60% of its global sales in the US market alone and is prescribed with far less frequency in the more cost sensitive UK, German and French markets.

Most chemotherapeutic agents are indicated for just one or two cancer types, but get significant off-label use once approved. Up to 60% of an oncology product's use is potentially for off-label indications. Much of this use is driven by the publication of data and/or approvals in other countries.

*Hormonal therapies*

Of the top-selling drugs in each major geographical region, *hormone therapies* contribute approximately one-third of the sales ex-US and one-fourth in the US. Hormone therapies for the treatment of cancer include Lupron (leuprolide/TAP), Zoladex (goserelin/Zeneca), Nolvadex (tamoxifen/Zeneca) and other agents used to treat hormone responsive diseases such as prostate and breast cancer. These agents are generally administered chronically and have reduced side effects compared to cytotoxic therapies. Sales of this category are driven primarily by Lupron and Zoladex. The US market has become increasingly cost sensitive in the Medicare sector, which accounts for over 70% of Lupron sales.

*Adjunctive agents*

The availability of effective *adjunctive agents* also allows the cytotoxic chemotherapeutic agents to be administered at higher doses and/or more frequently, or used in a more palliative role, since the adjunctive therapies can reduce the impact of the chemotherapy on the patient's quality of life. Agents in this class include immunostimulants, anti-emetics and bisphosphonates. The growth of this market is linked to the growth of the cytotoxic market, as the increased use of

cytotoxic agents drives an increased use in adjunctive therapy. The highest selling product in this class is Neupogen (filgrastim/Amgen) with 1998 sales of over \$1 billion.

#### *Biologic Therapy*

New therapies under development offer the promise of fulfilling several unmet needs in the treatment of cancer. Experts have predicted that in the future early therapy for breast cancer will be dominated by biological approaches, such as monoclonal antibodies (Herceptin/Genentech), which is widely thought to have strong market potential. Genentech recently reported strong second quarter sales of the product in the US of \$46.2 million, and it is estimated that if only half of US women with breast cancer who over-express this gene received Herceptin, sales would top \$600 million. In addition to monoclonal antibodies, other biological approaches include vaccines and gene therapy.

#### *Future Trends*

Emerging science in the past decade offers the potential to radically alter the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. New therapies offer the promise of fulfilling several unmet needs in the treatment of cancer. These include matrix metalloproteinase inhibitors (MMPis), continued expansion of biologics, photodynamic therapies (PDT), anti-angiogenics, and multiple drug resistance (MDR) modifiers. This market does not yet exist, though success of "cytostatic-like" treatments, such as hormonal therapies for prostate and breast cancer, suggests that the market potential for cytostatic agents could be significant.

#### *Competition*

The angiogenesis pipeline is very competitive, but this level of intensity is somewhat skewed by the large number of mechanistic approaches that are being claimed to demonstrate angiogenic activity. For the purposes of this summary, only those compounds considered true anti-angiogenic compounds have been included. Companies with compounds in clinical development include Genentech, Entremed, Sugen, TAP, Magainin and Pharmacia Upjohn.

#### **Angiogenesis Compounds in Clinical Development**

Compound	Indications	Company	Phase
Neovastat	Solid tumors	Aeterna	III
RhuMab VEGF	Cancer	Genentech	II/III
Vitaxin	Arthritis, psoriasis, CVR	Ixsys	II
SU-5416	Cancer	Sugen	II/III
TNP 470	Cancer, arthritis	TAP	II
Thalidomide	Cancer	EntreMed/BMS	I
Squalamine, squalus	Cancer	Magainin	I
RPI 4610	Cancer	Ribozyme	I
VEGF antagonist	Cancer, retinopathy	NeXstar	I
Angiostatin/Endostatin	Cancer	EntreMed	I

Due to the competitive intensity in this class, ABT-510 will need to demonstrate a significant clinical advantage in efficacy and/or side effects versus successful competitors to be commercially attractive.

### *Unmet Needs*

Cancer remains the second leading cause of death in the United States, Europe and Japan, and consequently, offers an attractive market opportunity for the pharmaceutical and biotechnology industries. This year about 563,100 Americans are expected to die of cancer, more than 1,500 people a day. In the US, 1 or 4 deaths is due to some form of cancer. In 1999, about 1,221,800 new cancer cases are expected to be diagnosed.

For most cancers, the level of physician satisfaction with current therapies is low. It has long been recognized by researchers, physicians, patients and family members that current treatment options may often be as devastating as the underlying disease.

Unmet needs in this market vary by tumor types and stages, with some tumors responding to treatment with better mortality and/or morbidity results than others. However, cancer is still treated as a terminal illness with significant shortcomings in present treatments. In general, unmet needs include:

Need	ABT-510 Attribute
Enhanced efficacy of therapeutic agents	Potential for enhanced efficacy
Reduced toxicity	Potential for reduced toxicity over current cytotoxic treatment
Improvements in drug administration	TBD
Improved target delivery of cytotoxics and novel therapeutics	Unknown
Proven outcomes data	Quality of Life and Pharmacoeconomics to be assessed

### *Considerations*

**Product Usage:** Physicians have indicated that they would use anti-angiogenic agents initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. Anti-angiogenesis agents are regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy. Of course, their ultimate use will depend on the benefit provided, which cannot be determined until clinical trials have been completed.

**Product Benefits/Efficacy:** Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. There is a great deal of enthusiasm for this mechanism in the scientific and lay audience. The concept is very intuitive. Products, such as ABT-510, that promise a clinical benefit without the usual toxic trade-offs associated with current chemotherapeutic agents, will be enthusiastically received by oncologists.

**Side Effects** The proposed safety profile of anti-angiogenic agents may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, anti-angiogenic agents may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance.

**Off-label use:** Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-



label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

*Other indications:* ABT-510 may be effective in other therapeutic roles, such as arthritic diseases and macular degeneration. These other indications may offer a commercial upside, through internal development or co-development/out-licensing opportunities.

*Competition:* While there are a relatively large number of angiogenesis inhibitors in development, it is unclear whether they will demonstrate a superior efficacy or side-effect profile vs. ABT-510. The mechanism of angiogenesis suggests that multiple anti-angiogenic approaches may be required to maximize the clinical benefit.

*COGS:* Initial estimates on finished cost of drug place it in the range of Lupron costs. Depending on final dosing requirements, the cost of this compound could become a significant obstacle. However, this will need to be considered in light of the pricing flexibility in the oncology market, where there is limited pricing sensitivity for products that are reimbursed. Any financial analysis will need to include royalty obligations to Northwestern University.

*Dosing:* There is still some uncertainty regarding the route of administration and feasible dosage forms for ABT-510. An "inconvenient" formulation leaves this product extremely vulnerable to competitors with more convenient dosage forms. A convenient dosage form, such as a monthly depot, will enhance product adoption over a less convenient form. However, the effect of the various dosage forms on product adoption will be dependent on the benefits the compound provides, side-effect profile and availability of competitive agents with more convenient dosage forms. For chronic therapy, convenience will play an important role in market penetration, given alternative agents. Although less convenient than oral therapy, parenteral therapy (depot, but not self-administered sub-cutaneous) is currently reimbursed by Medicare in the US. Over 60% of all cancer patients have Medicare as their primary healthcare coverage in the US.

*Development/Regulatory:* With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several anti-angiogenic agents in late stage development, Abbott can learn from their experience.

*Other Approaches:* Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

*Pricing:* The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.



*CONFIDENTIAL*

**ABT - 518**

OK

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**

**CONFIDENTIAL**

**ABBT 0006660**

**MMPI***Overview*

**Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.**

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer

animal models. ABT-518 is therefore a compelling development candidate with the potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients will begin December 2000.

#### *The market*

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

**Global Sales by Market Segment (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

**Sales by Region (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPIs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

#### *Compounds in Development*

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3<sup>rd</sup> or 4<sup>th</sup> to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

**MMPs in Clinical Development for Cancer**

<b>Compound</b>	<b>Company</b>	<b>Comments</b>	<b>Phase</b>
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

***Product profile***

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of the following benefits in at least one solid tumor type:  Increased survival Tumor regression Improved quality of life Increased time to tumor/disease progression	Provides more than one of the efficacy benefits outlined.
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

#### *Marketing overview*

**Product Usage:** Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

**Product Benefits/Efficacy.** Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

**Side Effects:** The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3<sup>rd</sup> or 4<sup>th</sup> MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go

decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

*Dosing:* Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

*COGS:* Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

*Off-label use:* Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

*Competition:* As the 3<sup>rd</sup> or 4<sup>th</sup> MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

*Development/Regulatory:* With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

*Other Approaches:* Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

*Pricing:* The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

*Dosing:* Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

*Clinical Studies*

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

*Patent Status*

The patent is estimated to expire in August of 2018.



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ABT – 627

*Am,  
Monthly highlights almost nothing  
for 627 re: the phase 2 study  
- Insert comment  
on Ph II results.*

## Descriptive Memorandum

November 2000

Abbott Laboratories

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**ABT-627***Opportunity Overview*

ABT-627 is an orally bioavailable endothelin antagonist with a high selectivity for the Eta receptor. The endothelins (ET-1, ET-2, ET-3) are a family of 21 amino acid peptides first identified in 1988. Endothelin is a potent, long acting vasoconstrictor produced by vascular endothelial cells. The known biological effect of ET-1 are believed to be mediated principally through the Eta receptor. These include potent and uniquely sustained vasoconstriction of vascular smooth muscle, positive inotropy of myocardium, and the stimulation of cell proliferation or the hypertrophy in vascular smooth muscle cells, cardiac myocytes, and fibroblasts.

In vitro studies in cultured cells have established that ABT-627 selectively binds to the Eta receptor, and that ABT-627 is a potent inhibitor of ET-1 binding to the Eta receptor.

Studies in cultured human prostate cancer cells and other cultured cells have shown that ABT-627 acts as a functional antagonist of ET-1, and these effects have been confirmed in vivo by assessing the effect of ABT-627 on the ET-1 induced pressor response in rats. Further animal studies have suggested that oral ABT-627 may be effective in the treatment of congestive heart failure, pulmonary hypertension, hypertension, arterial restenosis, and myocardial infarction.

In addition to literature and animal models supporting the role of endothelin antagonists in cardiovascular indications, data exists supporting the role of the ET-1 cytokine as a pathogenic mediator in cancer.

The current role of endothelin in the manifestations of metastatic prostate cancer (PCA) and other tumors have yet to be fully defined. However, Abbott scientists and thought leaders have made multiple observations about endothelin biology which suggest that endothelin may play a role in the biology and pathophysiology of metastatic prostate disease and other metastatic disease such as ovarian, cervical and renal tumors

ABT-627 has successfully completed Phase II trials for PCA, and the results demonstrate efficacy in hormone refractory PCA. It is expected that filing on ABT 627 will occur in US and ex-US 1Q 2004. An end of phase 2 meeting was very positive. Fast track designation and rolling NDA were granted. The compound is also in Phase I trials for other cancer types. Phase II studies in other cancer types will commence in 2Q01. Other indications outside of oncology are also being considered, to optimize the commercial potential of this asset.

*The US Market*

Prostate cancer is the most common cancer to strike nonsmoking men. The NCI estimates that there are over 1.7 million men living with prostate cancer in the U.S., and another 179,300 will be diagnosed in 1999. Nearly 80% of these cases are men over 60 years of age. It is estimated that the prevalence of prostate cancer is 380,000 in Western Europe and 45,000 in Japan. While the vast majority of these patients will be identified with potentially curable disease (25% in Stage I and 50% in Stage II) in the U.S., half of these patients will go undiagnosed until late stage disease in W. Europe and Japan. The skewed distribution of diagnosed cases ex-U.S. is largely due to less aggressive prostate cancer screening programs compared to the U.S.

Prostate cancer has seen few additions or innovations in treatment regimens in the past two decades. Treatments remain, in general, radical prostatectomy (RP) for localized disease, radiotherapy for locally advanced disease and hormone therapy for advanced disease. Patients receiving hormone therapy become refractory to this treatment after two to three years, although many will continue on hormone therapy. These hormone refractory prostate cancer (HRPCa)

patients usually have a life expectancy of approximately 12 months, and no existing standard of care exists for treating these patients. No therapy has shown a significant impact on survival in these patients, although some chemotherapeutic regimens may offer promise.

There is a general trend toward using hormone therapy in earlier stage patients. In some centers, patients are receiving hormone therapy prior to surgery or radiation, in an attempt to improve outcomes in these definitive treatments. Some thought leaders suggest that this earlier utilization has contributed to the overall mortality improvements in PCA. Studies are ongoing looking at different uses for hormone therapy, including intermittent therapy, in an attempt to improve outcomes and mitigate the morbidity associated with hormonal therapy,

Hormone therapy remains the mainstay of prostate cancer treatment in earlier stages. Chemotherapy, however, has gained additional attention in hormone refractory disease as new combinations and regimens offer the potential for greater therapeutic benefit with fewer side-effects. This trend will take several years before clinical trials are completed and community based oncologists adopt these regimens, so the current cytotoxic market in PCA is small.

The total dollar growth of this market has slowed as the two market leaders, Lupron (leuprolide/TAP) and Zoladex (goserelin/Zeneca), have experienced increased price pressures from managed care and Medicare. About half the states are currently reimbursing these therapies at a least cost option (only paying for the cheapest alternative), putting downward price pressures on Lupron (\$6,500/yr) to match Zoladex's (\$4,500/yr) lower price point. Thus, US Lupron dollar sales declined between 1997 and 1998, despite an increase in patient volume.

Growth has also stagnated due to a lack of innovation in this hormone dominated category. There have been few therapeutic advances in the treatment of PCA in the last 5 years.

The only chemotherapy approved for use in HRPc patients with pain is Novantrone (mitoxantrone/Immunex), but the marginal benefits this compound delivers is deeply undercut by its severe toxicities and a lifetime cap on dose. Novantrone and steroids significantly reduced the metastatic pain in 40% of patients, but it does not appear to provide a survival advantage. Novantrone is dosed by i.v. infusion every 21 days, at a cost of \$560 per treatment, or an annual cost of around \$8,000. Use of this agent is associated with significant side-effects, including myelosuppression, cardiac toxicity (which limits dosing) and nausea. It is this negative side-effect profile that inhibits the use of this agent in more patients. Only about 4% of U.S. HRPc patients received Novantrone therapy in 1998. Novantrone has not been approved ex-US.

Only about 17% of HRPc patients received any chemotherapy in 1998. The most common drugs included estramustine, paclitaxel and etoposide. These drugs continue to be some of the most studied compounds in HRPc ongoing research and represent the greatest short-term promise in the cytotoxic treatment of this advanced disease state.

**US Sales of Products to Treat Prostate Cancer**

Product	1997 Dollar Sales (MM)	1998 Dollar Sales (MM)	% chng '97-'98
Lupron (leuprolide/TAP)	\$650	\$667	2.6%
Zoladex (goserelin/Zeneca)	233	296	27.3
Casodex (bicalutamide/Zeneca)	58	68	17.24
Eulixen (flutamide/Schering)	74	67	-9.5
Novantrone (mitoxantrone/Immunex)	33	35	6.1
Nilandrone (nilutamide/Hoechst)	12	24	100
Emcyt (estramustine/Pharmacia/Upjohn)	8	14	75
Taxol (paclitaxel/BMS)	4	8	100
VePesid (etoposide/BMS)	5	4	-20
Others	27	31	14.8
<b>Total</b>	<b>1,104</b>	<b>1,214</b>	<b>10%</b>

Source: Tandem Research and Price Probe

**US Market Projections**

- Novantrone (mitoxantrone/Immunex) is currently the only product approved for the treatment of hormone refractory PCA with pain. It currently falls short on the market needs in terms of efficacy and side-effect profile.

Attribute	Novantrone Profile
Dosing	I.V. infusion cycles
Cost	Expensive, ~\$10,000/yr
Efficacy	Provides marginal improvements in quality of life
Reimbursed	Yes
Side-effects	Dose limiting toxicities
Promo Efforts	108 oncology reps
Targets	Oncologists

Several surveys indicate that there are over 100 compounds in preclinical and clinical development for prostate cancer and various solid tumors. The compounds listed in the appendix represent compounds that appear to offer the greatest promise and/or potential for competition for ABT-627. However, since the most likely use of ABT-627 will be in combination with best therapy, it is difficult to define the extent of competitive threat that any of these compounds represent. In general, other cytostatic agents probably offer the greatest threat as a replacement for ABT-627. However, even other cytostatic agents may be combined to maximize the activity of the various mechanisms.

To date, PPD is aware of only one other endothelin receptor antagonist in development for cancer, from Yamanouchi, which began Phase I studies in the Fall of 1999. ABT-627 is still poised to be the first endothelin receptor antagonist to reach the market for oncology.

*Scientific Rationale for ABT-627*

There are relatively low hurdles for entry for a product to treat hormone refractory prostate cancer, as no truly effective agents presently exists. Quality of life is paramount in this population, followed by improvements in disease progression and survival. Quality of life parameters could include an impact on pain/or delay in pain onset or other performance type measures of daily activities. As all hormone therapy ultimately fails, a product that delays disease progression is needed.

Unmet Need	Pipeline Impact
Improvements in QOL	<ul style="list-style-type: none"> <li>• ABT-627's profile goal is to provide improvements to a patient's QOL or blunt a decrease in QOL</li> <li>• Cytotoxic agents rarely have significant positive impacts on QOL</li> <li>• Other cytostatic agents may offer this benefit</li> </ul>
Improvements in survival	<ul style="list-style-type: none"> <li>• It is unlikely that improvements in survival will be seen in our current trials</li> <li>• Cytotoxic agents may offer a survival advantage, perhaps in combination with ABT-627</li> </ul>
Improvements in time to disease progression	<ul style="list-style-type: none"> <li>• Cytostatic and cytotoxic agents offer the greatest promise for this benefit</li> </ul>

Our objective is to provide physicians and patients with a novel option for the treatment of hormone refractory prostate cancer, distinguish ABT-627 from current cytotoxic therapies and encourage the treatment of advanced prostate cancer patients currently only receiving hormonal therapy.

ABT-627 will be positioned as a physician and patient-friendly choice for advanced prostate cancer patients who have failed hormone therapy. ABT-627's novel mechanism of action provides a delay in disease progression and a positive impact on QOL. The oral, QD dosing enhances compliance and minimizes disruptions to daily living.

The message will focus on 3 key attributes:

- Efficacy (defined as increased time to tumor progression) in a patient group with few options
- Improvements in quality of life
- Convenience

Physicians no longer have to choose between *treating* advanced prostate cancer patients and a patient's quality of life. ABT-627 has a positive impact on disease progression and symptoms associated with quality of life, without the baggage of significant side-effects or the inconvenience of parenteral administration associated with current therapy choices.

This message expresses the key features of the agent in terms of patient benefits, as opposed to emphasizing the scientific/clinical aspects. Since prostate cancer is a terminal disease with a relatively long time for disease progression, the quality of a patient's life becomes even more critical. Especially in cancer treatment, where the therapy can often feel worse than the disease, the benefits that ABT-627 will bring, coupled with its benign side-effect profile, will have a significant impact on prostate cancer patients' lives.

### Clinical Studies

Phase II trials have been completed and the data are being analyzed. Preliminary analysis suggests a positive impact on disease progression in hormone refractory PCA.

### Patent Status

The U.S. patent was filed in May, 1995, issued on June 16, 1998 and expires June 16, 2015. Patents for international locations are pending under the Patent Cooperation Treaty.

### Key Prostate Cancer Competitors

Product	Company	Phase	Projected NDA Filing	Description	Anticipated impact on ABT-627
AG 3340	Agouron	III	2000	MMPi	In combination with mitoxantrone/prednisone. Unknown impact.
Marimastat	British Biotech	II	2001	MMPi	Side-effect profile significantly worse than ABT-627. Probably minimal impact.
SU 101	Sugen	I/II	2002	PDGF TK antagonist	Phase III in combination with mitoxantrone set to start in 1999. Uncertain impact.
AR 623	Aronex	II	2002	All-transretinoic acid	IV liposomal form of ATRA. HRPc trial began November 1998. Probably additive.
MGI 114	MGI Pharma	II	2002	Alkylating agent	Lead compound in acylfulvenes. Fairly toxic. Probably additive.
Liposomal Encapsulated doxorubicin	NeoPharm and P&U/Alza and others	II	2002	Anthracycline	Various forms being developed by various companies. Probably additive.
Sataraplatin	BMS	III	2000	Platinum complex	Oral platinum analog w/toxicities comparable to carboplatin. Probably additive.
Taxol	BMS	II	2001	taxane	In various combinations with other chemo agents. Probably additive.
Taxotere	RPR	II	2001	taxane	In various combinations with other chemo agents. Probably additive.

*CONFIDENTIAL*

**ABT - 751**

p<sup>2</sup>

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**



## ABT-751

### Opportunity Overview

Cytotoxic agents and hormones constitute the dominant classes of drugs available to treat cancer and are responsible for 96% of the total market. Since 1993, Taxol, a taxane developed and marketed by BMS, has been widely used. Another taxane, Taxotere, developed and marketed by Aventis, was launched in 1996. Combined worldwide sales of these two products were of nearly \$2 Billion US in 1999. Clinically, the development of drug resistance is the primary factor that limits the efficacy achievable with these drugs.

Abbott's anti-mitotic agent (ABT-751) is a novel, oral cytotoxic agent that acts by a mechanism similar to that of the taxanes but retains activity against taxane resistant cells. ABT-751 binds to the colchicine site on tubulin and inhibits the *in vitro* polymerization of microtubules. The interference with normal microtubule dynamics leads to a block in the cell cycle at the G2/M phase that ultimately results in the induction of cellular apoptosis. ABT-751 is a potent antimitotic agent that inhibits the proliferation of a broad spectrum of human tumor derived cell lines including those that are paclitaxel and doxorubicin resistant due to the multidrug-resistant (MDR) phenotype or other genetic changes.

ABT-751 demonstrated impressive oral antitumor activity when evaluated in both synegeic and human xenograft tumor models. The antitumor response was independent of the MDR status of the model, consistent with the activity observed in cell cultures. In sharp contrast with other cytotoxic drugs, the dose of ABT-751 determined to be the maximum tolerated on a q.d. 1-5 schedule could be administered for an extended period (q.d. 1-21 or q.d. 1-28) resulting in a dramatic enhancement of the antitumor activity. These results suggest that the colchicine site ligands, such as ABT-751, will exhibit a broad spectrum of activity that will be distinct from that of other classes of antimitotic drugs. Oral availability of the compound is high. Taxol and Taxotere, in contrast, have no oral bioavailability.

*amended sentence*

The most significant finding in toxicology studies was a change in systemic and pulmonary vascular resistance following intravenous infusion of ABT-751 to anesthetized dogs. These effects led to an inverse response in cardiac output. Similar changes were observed following infusion of a structurally unrelated colchicine-site ligand, and therefore most likely represent a class effect. ABT-751 has been administered to patients, and plasma concentrations were achieved that are equivalent to those that affected systemic resistance and cardiac output in the anesthetized dog. No adverse cardiovascular effects were observed, and ABT-751 was well tolerated following daily administration for 5 days. At present, it is predicted that ABT-751 will be administered to patients intermittently. The risk posed by the repetitive and intermittent vasoconstriction predicted by these studies will be thoroughly quantified by toxicology studies focusing on vascular pathology.



# PART 2

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market

**Global Sales by Market Segment (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

**Sales by Region (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

This growth of the cytotoxic segment has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Uptake of these newer agents, however, can be dependent on the cost sensitivity of the local market.

The clinical targets identified for this compound include late stage breast cancer, late stage NSCL cancer (on-label), with late stage ovarian and pancreatic cancer as additional cancer types where efficacy has been demonstrated, but not filed. This product may also be potentially efficacious in cancers such as gastric, colorectal, prostate, bladder, esophageal, hepatocellular (ex US), lymphoma, and leukemia. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key competitive products by indication (US data only):

**Late Stage Breast**

Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

**Late Stage NSCL**

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

## Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

## Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

*Compounds in Development*

ABT-751 induces a mitotic block by binding to the colchicine site on tubulin and thereby affecting tubulin polymerization. There are no currently available drugs which function by the mechanism described above. However, vinca alkaloids and taxanes fall into the broad category of anti-mitotics although they produce the anti-mitotic effect through different mechanisms. The following table summarizes anti-mitotic compounds in development.

Company	Compound	Indication	Status of compound	Status of project
<b>Colchicine-site ligands</b>				
Oxigene	combretastatin-A4 phosphate	Tumor vasculature	Phase I	active
Tularik	T138607 (phosphate prodrug)	Cancer (unspecified)	Phase I	active
Tularik	T900607	Cancer (unspecified)	Preclinical	active
ICI/CRC	Amphethinile	Cancer (unspecified)	Phase I (abandoned 1988)	inactive
Wellcome Research	1069C	Cancer (unspecified)	Phase I (abandoned 1996)	inactive
NIH	Trimethylcolchicinic acid	Various tumors	Phase I (1990, abandoned)	inactive
Parke-Davis	CI-980	ovarian, colorectal	Phase II (abandoned 2000)	inactive
<b>Vinca alkaloid-site ligands</b>				
BASF	LU103793 (dolastatin 15 analog)	Cancer (unspecified)	Phase II (abandoned)	active
Servier	vinxaltine	Cancer (unspecified)	Phase I	unknown
NCI	dolastatin 10	Adv. Cancers	Phase I	unknown
Teikoku Hormone	TZT-1027 (dolastatin 10 analog)	Cancer (unspecified)	Phase I (Jpn)	unknown
Lilly	LY 355703 (cryptophycin 52)	Cancer (unspecified)	Preclinical	unknown
Takeda	maitansine	Cancer (unspecified)	Preclinical	unknown
<b>Microtubule stabilizing agents (non-taxanes)</b>				

Soc. Biotech. Res/ Bristol-Myers Squibb	epothilone	Cancer (unspecified)	Preclinical	active
Bristol-Myers Squibb	eleutherobin	Cancer (unspecified)	Preclinical	active
Pharmacia & Upjohn	sarcodictyins	Cancer (unspecified)	Preclinical	active
Takeda	GS-164	Cancer (unspecified)	Preclinical	active

The novelty of this mechanism offers the promise of differentiation that will diminish the threat from potential competitors. However, this novelty is balanced by the similarity to current mechanisms, such as taxanes and vinca alkaloids, which suggests the promise of clinical efficacy. With the opportunity to be first or second to market with an agent that binds to the colchicine site, the competitive situation seems modest.

*CONFIDENTIAL*

# Farnesyltransferase Inhibitor

OIC

P 3

## **Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**

### *Overview*

The Ras genes were the first oncogenes of mammalian origin to be discovered. Intensive research over the last decade has led to the elucidation of the normal function of cellular Ras protein, the role of Ras mutations in oncogenic transformation, and the identification of molecular targets, such as the enzyme farnesyltransferase, for inhibiting Ras activity. Although farnesyltransferase inhibitors (FTIs) were initially designed with the intention of inhibiting the posttranslational prenylation, and hence function, of Ras, it is now becoming apparent that farnesylated proteins other than Ras (e.g., RhoB) are also critical for malignant growth and may be the relevant target for inhibition of farnesylation. While it remains controversial whether blocking Ras activity or altering the RhoB prenylation status is the actual function of an FTI, these agents, exemplified by ABT-839 and FTIs in the clinic, exhibit remarkable anticancer activity against a wide variety of tumors in preclinical models. The current FTI program reaches DDC status in January, 2001.

Abbott evaluated one FTI, ABT-839, in normal volunteers, but decided to discontinue development of this drug due to its poor pharmacokinetic profile. Invaluable experience was gained, however, from both the preclinical and clinical studies with this compound. Abbott's second-generation series are novel, patentable structures that exhibit significantly improved potency and oral bioavailability.

There continues to be tremendous enthusiasm in the medical community and pharmaceutical industry for this mechanism of action. Farnesyltransferase inhibitors have demonstrated impressive antitumor activity in preclinical models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at the maximal tolerated dose. These agents appear to inhibit angiogenesis and, consistent with this activity, minimal resistance has been observed in preclinical models. The potential also exists for synergistic activity in combination with cytotoxic chemotherapy.

### *The market*

Cancer remains the second leading cause of death in the US, and consequently is an attractive market opportunity for the pharmaceutical/biotechnology industries. Approximately 40% of all Americans will develop cancer in their lifetime.

The worldwide cytotoxic and hormonal cancer therapies market is highly fragmented with only BMS and Zeneca holding a greater than 10% market share. Although the market is not concentrated, the field is highly competitive with more than 60 companies focused on the cancer research area. The growth of the oncology market is fueled by increasing disease incidence, new product entries, new therapeutic approaches, a growing adjunct therapy market that expands the number of patients eligible for chemotherapy, and intensified research competition. The data in Tables 1 and 2 summarize the value of the current oncology market. A great deal of uncertainty surrounds the concept of cytostatic treatment of cancer. Conceptually it may transform the way cancer is treated, allowing patients longer disease free survival and improved quality of life. However, at this point in development, this paradigm does not exist in cancer. Considering market, clinical and patient dynamics factors, breast, colorectal, prostate and non-small cell lung cancers are the most attractive targets for development.

**Table 1. Global sales by market segment (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

**Table 2. Sales by region (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the FTI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, FTIs will probably be adopted initially as add-on <sup>to</sup> the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

## Late Stage NSCL

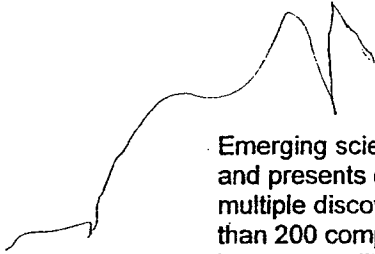
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

## Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

## Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72



Emerging science within the past decade has radically altered the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. Abbott has multiple discovery cytostatic targets, which may improve effective, but we are not alone: more than 200 compounds from other players are in development. The goal of cytostatic therapy is to improve quality of life, controlling the disease and transforming aggressive treatment to a chronic condition, which has been compared to the impact of protease inhibitors on the course of HIV.

*Clinical Studies*

Considering all the factors, market, clinical and patient dynamics, breast, colorectal, prostate and non-small cell lung cancer appear to be the most attractive targets for development. The development of cytostatic agents faces a number of challenges as regulatory agencies and physicians evaluate the new emerging paradigm of cancer therapy.

Despite the enormous medical need, drugs for chronic treatment/disease stabilization and improved quality of life for cancer patients do not yet exist. Correspondingly, animal models test efficacy that has not yet been validated as predictive of response in humans. Medical oncologists have historically depended on determination of maximum tolerated dose and response manifested by tumor shrinkage for cancer drug development. These parameters are not relevant to novel "cytostatic" agents. Combination with conventional cytotoxic drugs will be required in the near term and will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.



**Competition:****Within Project Approach**

Company	Compound	Indication	Status of compound	Status of project
Janssen Pharmaceutica	R-11577 (A-251076)	Cancer (unspecified)	Phase III	active
Schering-Plough	Sch66336 (A-285622)	Cancer (unspecified)	Phase II	active
Merck	L-778123	Cancer (unspecified)	Phase I (i.v.) abandoned	unknown
Bristol-Myers Squibb	BMS-214662	Cancer (unspecified)	Phase I	active
LG Chemical	LB 42908	Cancer (unspecified)	preclinical	active
Rhône-Poulenc Rorer	quinuclidine derivatives	Cancer (unspecified)	preclinical	active
Pfizer	unknown structure	Cancer (unspecified)	preclinical	active
Parke-Davis	unknown structure	Cancer (unspecified)	preclinical	active
Roche	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Eisai	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Banyu	FPP mimetic	Cancer (unspecified)	preclinical	unknown
ISIS	ISIS-2503 (ras antisense)	Cancer (unspecified)	Phase I	active

**Within Therapeutic Area**

Approach	Selected Compounds	Company(ies)	Status
antisense	ISIS 3521, ISIS, 5132	ISIS	phase I
cytotoxic agents	camptosar, CI-980, faestron, Genzar, Hycamtin, Indarubicin, Novantrone, Onconase, Capecitine, Tomudex	P&U, Warner-Lambert, Schering, Lilly, SKB, P&U, Immunex, Alfacell, Roche, Zeneca	most phase III
differentiation	targretin, panretin, 5-azacytidine	Ligand, NCI	Ligand in phase I/III
drug resistance modifiers	VX-710, 776C85, RMP-7, CT-2584	Vertex, Glaxo Wellcome, Alkermes, Cell Therapeutics	Vertex in phase II
gene therapy	Onyx-015, , MDRx1, GLI-328, IL-2, GV-1301	Onyx, Introgen, Therion Biologics, Theragen, Genetic Therapy, Cyclacel, RPR Gencell, GeneMedicine, Titan, etc	Restricted to accessible cancers. Most advanced: Phase I/II
hormonal therapy	Zolodex, arimidex, droloxifen, Oncolar, Rivizor, Casodex, rogletimide	Zeneca, Pfizer, Novartis, Janssen, US bioscience	most phase III
immunotherapy			
antibodies	IDEC-Y2/n2B8, anti-HER2, anti EGFR	IDEC, Genetech, ImClone	IDEC recently approved, others phase III
cytokines	IL-12, IL-4, Proleukin, Roferon-A	Roche, Schering, Chiron, Roche	phase III
vaccines	rV-gp100, Genevax, MGv	Apollon, Therion, Progenics	phase I, II
photodynamic	photofrin, promycin	QLT photo, Vion	phase III
radiation sensitizers	Neu-Sensamide, radinyl	Oxigene, Roberts	phase II, III
metalloproteinase inhibitors	marimastat, AG-3340, CGS-27023A	British Biotech, Agouron, Novartis, Bayer	BBT in phase III
angiogenesis inhibitors	TNP-470, SU-5416, anti VEGF-mAb, thalidomide, DC101	TAP, Sugen, Genentech, Entremed, ImClone, etc	see angiogenesis project review for details

### Competitive Analysis

The project is on par with others in the industry. While second generation Abbott compounds are not yet in clinic, all of the compounds from other companies that are in clinical trials have deficiencies. While the Schering compound has the best oral PK profile, it is not particularly potent. The Janssen compound is potent, but has a poor PK profile. The Merck compound exhibited QTc prolongation and development has been stopped. The Bristol Myers Squibb compound, BMS-214662, which is in phase I, is an *in vitro* submicromolar inducer of apoptosis in human tumor cells and appears to be the most potent inducer of apoptosis of the known FTIs. This compound could have a different mechanism of action from the classical FTIs and have its own liabilities. LG42908 from LG Chemical is potent FTI and has good oral bioavailability (F= 91% in monkey), however, it's a CYP3A4 inhibitor and will have significant drug-drug interaction liabilities. Extensive preclinical pharmacology at Abbott has defined optimum parameters for a FTase inhibitor that may not be known to our competitors, or be achievable with the current generation of FTIs. We anticipate that the Abbott compound will be improved over competitors' compounds with respect to potency, oral bioavailability, half-life, toxicity, efficacy, angiogenesis inhibition, and lack of resistance.

### Patent Status

Several patents cover Abbott's FTI.

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ABT-594

**Descriptive Memorandum**

November 2000

Abbott Laboratories

My only concern  
here is that on p. 2 & 3  
we may cause Hamner to  
conclude the pain relief  
is not worth the medical use  
of generics. A sentence  
stating how well received  
a new agent  
would be could be  
helpful. could be

CONFIDENTIAL

ABBT 0006685

**ABT-594 Opportunity Overview**

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth. Of even greater impact on total market sales, most of the agents used to treat this population, with this exception of Neurontin, are low-cost, generic products.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

*There is an unmet <sup>market</sup> need for ~~new~~ novel neuropathic pain treatments and ABT 594 is likely to be well received in this arena.*

**Market Size / Prevalence**

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

**Competition, Current Marketed Products:**

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
<b>TOTAL</b>	<b>12.5</b>	<b>5.6%</b>	<b>N/A</b>	<b>N/A</b>
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
<b>TOTAL</b>	<b>\$351</b>	<b>21.7%</b>	<b>\$140</b>	<b>10.1%</b>
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

**Competition, Products in Development**

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through $\alpha 2\delta$ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				



Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

### Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events.  Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimocromol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.



## **Product / Development Background**

### *Scientific Rationale for ABT-594*

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

### *Clinical Studies*

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients are anticipated to be included in the study.

**Patent Status**

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing composition of matter coverage for a large class of structurally related neuronal nicotinic receptor analogs, which encompasses ABT-594 (5246.U.S.) The original filing date for this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 under this patent is June 2016.

An additional application (6013.US.01) which includes a use claim for ABT-594 species in analgesia was filed in September 1997, with subsequent divisional filing of ABT-594 species composition of matter. Despite this later composition of matter filing for the species claim, it is likely that a "terminal disclaimer" will be necessary that dates the composition of matter claim back to the original genus patent (5246.U.S.) We have paid the issue fee for this patent on July 19, 2000, and are anticipating the patent to issue 90 - 120 days from that date. If this patent is allowed, it will provide 20 years from date of filing for the use of ABT-594 in analgesia, which will extend the patent life of ABT-594 to September 2017.

The original application providing generic composition of matter coverage was filed broadly ex-U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

As additional information regarding potential uses for ABT 594 is gathered, applications to expand the scope of ABT 594's patent will be submitted. A task force consisting of members of NUDR, the Analgesia Venture, New Product Development, the Neuroscience Franchise, and the Abbott Patent Department will conduct periodic review of the patent.

**Considerations**

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

*Label Strategy:*

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
  - 2) Treatment of post-herpetic neuralgia
  - 3) Treatment of neuropathic pain
  - 4) Treatment of chronic pain
  - 5) Treatment of cancer pain

*Cost of Goods Sold:*

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

*Pricing:*

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

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**ABT – 492**

*This seems to be far  
more complete than most of  
the other memoranda in  
some cases.*

**Descriptive Memorandum**

*November 2000*

**Abbott Laboratories**

November 1st, 2000

Hancock\_ABT 492

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ABBT 0006694

**ABT 492***Overview*

The commercial success of fluoroquinolones such as ciprofloxacin and levofloxacin, along with the desire to further improve the properties of these compounds (microbiological spectrum and safety, for example) has led to fierce competition to identify analogs with superior therapeutic properties. In addition, the development of resistance to present antibiotics will drive a continued need for new agents. Goals for a quinolone antibiotic include broad-spectrum indications equal to trovafloxacin, antibacterial activity comparable to trovafloxacin, tolerability comparable to levofloxacin, oral and intravenous formulations, once daily dosing, length of treatment equal to moxifloxacin, and an acceptable cost of goods. ABT-492, an in-licensed compound from the Wakunaga Pharmaceutical Co., is being developed for evaluation to meet these goals.

The *in vitro* antibacterial activity of ABT-492 was consistently more potent than trovafloxacin against most quinolone-susceptible pathogens, including species responsible for community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. The compound has potent activity against multidrug-resistant *S. pneumoniae* (penicillin-, macrolide-, tetracycline-resistant) and retained activity against *S. pneumoniae* strains resistant to other quinolones including trovafloxacin. ABT-492 was also highly active against anaerobes and ciprofloxacin-susceptible *P. aeruginosa*. ABT-492 was as active as trovafloxacin against *C. trachomatis*, indicating good intracellular penetration. Thus, ABT-492 is likely to be a useful broad-spectrum antibacterial agent. The enhanced antibacterial activity of ABT-492 relative to ciprofloxacin, levofloxacin, and trovafloxacin is likely to be explained, in part, by its potent interactions with bacterial topoisomerases. ABT-492's equivalent activity against both the DNA gyrase and the topoisomerase IV of pathogens, give ABT-492 a potential for decreased development of resistance.

The *in vitro* potency data suggests that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin and superior to levofloxacin. In addition, ABT-492 was consistently more potent than trovafloxacin against MRSA and vancomycin-resistant enterococci. In both these cases, however, therapeutic utility remains to be assessed in the clinical setting.

*S. pneumoniae* was chosen as the dose-defining pathogen since it is the key pathogen in severe respiratory tract infections and treatment of infections caused by this pathogen has traditionally been a weakness of most quinolones. For treatment of fluoroquinolone-susceptible *S. pneumoniae* respiratory tract infections, oral dosing may be similar to trovafloxacin based on data generated in lung infection models. Because of the excellent potency of ABT-492 against fluoroquinolone-resistant *S. pneumoniae* with an MIC<sub>90</sub> of 0.12 µg/ml, this group of emerging strains may be targeted as a key differentiation point from other quinolones. Also, data from the thigh infection model suggests significantly greater efficacy for ABT-492 than for trovafloxacin.

*The Market*

ABT-492 is broad-spectrum anti-infective agent with potential application across a broad range of indications, including respiratory infections, genito-urinary infections, and skin/soft tissue infections. It is assumed that a pediatric formulation would not be a part of the primary development plan due to the known adverse events caused by quinolones in pediatric populations. Nonetheless, reports of quinolone pediatric development has been reported (gatifloxacin), hence the pediatric market should be regarded as a potential upside for this quinolone should its safety profile merit its use in pediatrics.

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**Current Treatment Options**

Class	Mechanism of Action	Comments
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains and modification of penicillin-binding proteins.
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; <i>H. flu</i> activity continues to be class weakness, along with GI adverse events, drug-drug interactions, & taste perversion
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in a broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram- profile will be used primarily in nosocomial setting

**U.S. Market**

1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The IV market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

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Quinolones have seen dramatic growth, with oral and IV sales growing at 17% and 16% compound annual rates, respectively, from 1995-1999. This growth is a function of the newer quinolones successfully penetrating the RTI segment, which was initiated with the 1997 launches of Levaquin and Trovan (withdrawn) and continues with the recent introductions of Tequin and Avelox.

#### **Ex-U.S. Market**

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. The tab/cap represents the largest segment, with sales of \$9.4 billion on 770 MM TRX. TRX growth has been flat, with a 1996-99 CAGR of 0.5%; the use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-US, the quinolone class accounted for 8% (62MM) of total tab/cap market prescriptions and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-US, with approximately 47% of the quinolone market Rx's (29MM) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market, and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-US levofloxacin sales (\$370MM).

1999 Ex-US Tab/Cap Market						
Class	Sales (\$MM)	Sales Share	Sales CAGR '96-'99	TRXs (MM)	TRX Share	TRX CAGR '96-'99
Market	\$9,348	—	3.6%	770	—	0.8%
Quinolone Class	\$1219	13%	-12%	62	8%	NA
Cipro	\$530	5.7%	4.9%	29	3.8%	NA
Levaquin	\$466	5.0%	NA	18	2.3%	NA
Trovan	\$12	0.1%	NA	0.5	0.1%	NA

#### **Competition**

The anti-infective pipeline is very competitive, but most of the competition is focused on improving the activity and safety of the quinolones. Ketolide development is the only other area of activity which is in late stage of development. The quinolone compounds in present development may fall out because of safety or lack of activity against resistant pathogens.

Competitive Analysis – Emerging Competition					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Ketek (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.

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<b>Competitive Analysis – Emerging Competition</b>					
<b>Product</b>	<b>Company</b>	<b>Class</b>	<b>Phase/Estimated Time to Market</b>	<b>Country</b>	<b>Comment</b>
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to quinolones for MRSA; highly potent vs. RTI pathogens <i>H. flu</i> , <i>M. cat</i> , and <i>S. pneumo</i> and UTI pathogens <i>E. coli</i> and <i>P. mirabilis</i> , CRSP; potency > spar, trov, grepa and ≥ moxi; activity vs. <i>P. aeruginosa</i> ?; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; 700 patient database
Sitafloxacin	Daiichi Seiyaku	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Very potent MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC; will likely be target to severe rather than community infections
Ecenofloxacin	Chiel Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to lome and oflo vs. <i>P. aeruginosa</i> . T <sub>1/2</sub> = 14-19 hr; will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G <sup>+</sup> /–; excellent activity against <i>H. flu</i> , <i>c. jejuni</i> , <i>M. pneumo</i> , and <i>C. trachomatis</i> ; greater potency than cipro; t <sub>1/2</sub> ~7 hr; BA~80%
T-3811	Toyama/BMS	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency ≥ trova, STFX & HSR-903

#### Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

ABT-492 is one of the most active agents against the resistant organisms. It has indications that will have a low propensity for the development of resistance. ABT-492 will be developed to maximize any opportunities to shorten therapy. ABT-492 was chosen from hundreds of quinolones because of its potential to be well tolerated and safe in humans. ABT-492 will have few interactions with other drugs.

<b>Unmet Need</b>	<b>Pipeline Impact</b>
Activity against resistant organisms	<i>Strep. pneumo</i> , MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant <i>Strep. pneumo</i> strains; quinolone-resistant <i>Strep. pneumo</i> may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety

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ABBT 0006698



	profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

### Considerations

**Product Usage:** Physicians are likely to use ABT-492 for the sicker patients with the most difficult infections to treat. In the outpatient arena it will be used to treat community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis in the older patients with an underlying illness. It will also be used in the hospital for the community-acquired pneumonia patient who requires hospitalization and for serious nosocomial infections.

While many regard quinolones as agents that should be reserved for 2<sup>nd</sup> line use, their activity against *H. influenzae* and resistant *Strep. pneumoniae* (which current macrolides do not offer) have resulted in a high level of acceptance for empiric 1<sup>st</sup> line use. The improved safety profiles of several recent quinolones have facilitated their use as 1<sup>st</sup> line agents. Provided that ABT-492 is proven to have a benign safety/adverse event profile, it will likely receive usage in both 1<sup>st</sup>-line (non-severe) and 2<sup>nd</sup>-line (severe) infections.

**Side Effects:** The quinolone class has potential prolongation of the QT interval and other cardiovascular effects. There is also increased regulatory scrutiny due to recent quinolone withdrawals from international markets. ABT-492 has been evaluated in the standard *in vivo* models used to evaluate QT interval potentials of other antibiotics and has shown no evidence of increasing QT. Also, compared to marketed quinolones, preclinical studies show no evidence or no increase incidence of CNS drug concentration (ie. less potential for dizziness); phototoxicity; and liver toxicity.

**Off-label use:** It is difficult to predict at this time what off-label uses will be seen for this compound. Initial development will be for the more common respiratory, urinary tract, skin, and hospital infections. Other indications will be evaluated after the primary approval of this compound. Many of the secondary indications will get usage before we have regulatory approval.

**COGS:** The initial cost of goods is in \$6000/kg range, but will come down rapidly after the initial starting materials are determined. At time of launch ABT-492 will have a cost of goods in the \$1500/kg range which is competitive compared to other quinolones and other new antibiotics.

**Dosing:** Based on animal models and the *in vitro* activity of ABT-492 the dose for most oral indications will be in the range of 100 to 200 mg give once daily.

**Development/Regulatory:** Anti-infective compounds are well understood by regulatory agencies globally and they have clearly defined clinical development path and regulatory guidelines for reference. Abbott Laboratories has been in this arena for many years and has experience with the FDA and European regulatory agencies and so the hurdles to development are well know.

**Other Approaches:** Because of the well defined development guidelines there are not many options. The major development options are in dosing regiments. ABT-492 is a very potent drug which has demonstrated rapid killing of pathogens *in vitro* and *in vivo*, and the development plan will attempt to shorten treatment durations to increase the competitive advantages of this activity.

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ABBT 0006699

*Pricing:* The community infection market is quite competitive from a pricing standpoint, with recent quinolones priced at approximately \$45 per 5-7 days of therapy. The pricing strategy will depend on strengths/weaknesses of the ABT-492 product label, the competitive landscape at launch, and the managed care environment, but current pricing assumption is parity for ABT-492 with respect to other quinolones.

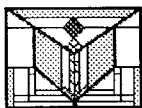
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ABBT 0006700

**AL**



Carol S  
Meyer/LAKE/PPRD/ABBOTT  
09/20/2001 01:29 PM

To: Stan Bukofzer/LAKE/PPRD/ABBOTT  
cc:  
bcc:  
Subject: Re: Portfolio issues update

I made my corrections in red. I only have one more issue to clear up with Bill. The PARD numbers on the detail don't match and I think he has an error in the total cost, but I'll verify and let you know  
Stan Bukofzer



Stan Bukofzer  
09/20/2001 12:27 PM

To: Carol S Meyer/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: Portfolio issues update

----- Forwarded by Stan Bukofzer/LAKE/PPRD/ABBOTT on 09/20/01 12:27 PM -----



Stan Bukofzer  
09/19/01 12:32 PM

To: John M Leonard/LAKE/PPRD/ABBOTT  
cc:  
Subject: Re: Portfolio issues update

John  
Thanks for the opportunity to address the questions. All answers in Blue.  
Corrections

John M Leonard

John M Leonard  
09/18/01 11:24 PM

To: Stan Bukofzer/LAKE/PPRD/ABBOTT  
cc: Eugene Sun, Kenneth Stiles, Thomas Woidat, Thomas Lyons  
Subject:

In preparation for Friday, I have some questions that follow. You can send answers in advance of the meeting or bring them with you.

Thanks,  
J

ABT-773

(see the "2002 PLAN Development Summary " cover sheet)

Clinical Program -

I assume the accruals for 219 run through 3/02 and not 03  
Yes, this is a typo, should be ending enrollment in 3/02

Of the clinical programs with substantial activity this year, which can have costs accelerated in to 2001?

We can try to accelerate spending in 2001. Dependent on start of patient enrollment .

I do not have a grants page . Therefore, can you give me a quick summary of per patient costs of the studies that will be running next year? I am particularly interested in costs per patient by indication by investigator grants as well as CRO costs .



Clinical Grants 2002 9.19.01. In case you cannot open the project file, the direct CRO costs are approximately \$ 5200 per patient on average for CAP and Sinusitis . Investigator grants vary from \$1700-3600 for sinusitis and \$ 5000-\$1800 for CAP depending on area of world . It is fiercely competitive to recruit these patients and we pay at the lower end of market .

I like the graph describing bulk drug costs . Some text will be helpful to explain it, however . Please mention the ultimate target costs at launch (bulk and then finished product ) . Also, we are spending \$9.8MM on process chemistry, not an inconsequential amount . Please summarize what this is on a sheet to add to the material prepared . Who is working on this, what are they doing, what are the deliverables, and why are we spending so much? What will we do with the material that they produce?



773 bulk drug timeline 9.7.01.PC

Campaigns 17 & 18 are development /engineering runs postponed from 2001 to 2002 based on the revised filing date . Yield is estimated to be 670kg for these 2 campaigns, cost is \$ 2.130M. 400kg of these campaigns will be used to run the Demonstration batch for the US mfg site, AP 16. Also in 2002, Intermediate steps 3-5 will be run in -house or at a vendor to prepare for the Bulk Drug validation runs (4) to be run in 2003, cost is \$ 1,950M. Costs for these intermediates in 2002 will be partially credited back when validation lots are used as part of product for sale . Remaining costs are: \$3,811M for process chemistry headcount to do process justification for the NDA, \$ 1,459M for Analytical support and \$ 427M for Pilot plant and vendor development .

We need more details on formulation and analytical . What is being done for \$ 8MM? I know that we will get stability as part of the answer, but this needs to be explained . Is anyone looking at what the stability program is and how much it costs? Do we really need to do everything that is being done?



PARD 773.xls

The stability program supports the filing strategy of 4 finished product NDA lots on stability to represent all four Vendors supplying step 2 intermediate for bulk drug . This was done to support step 2 as a starting material in case the regulatory agencies did not agree to our step 5 starting material justification . Our stability matrix supports bottle and blister configurations requested by US and AI marketing groups .

Costs for IDC for 2001 to support the U.K. final product scale up activities was \$ 1,791M. This should be reflected in Other CMC costs for 2001 (the Development Cost Summary listed these costs in Other Support Costs incorrectly ) . All activities to support the U.K. scale up are transferred to PARC in 2002. These costs are now part of the PARC budget for 2002. Total Tablet Formulation /Analytical budget in 2001 was \$7015M. In 2002 Tablet Formulation /Analytical budget is \$6511. PARC costs for IV are \$ 117M.

I have a problem with costs listed as "other." In Tox, there is \$ 2.2MM and under "other" there is yet another "other" at \$3.2MM. Therefore, "other on this program totals \$ 5.4MM out of a total of \$77.1MM. We need to pin this down .

Drug Safety "Other" costs consist of Clinical Drug Analysis \$1,690M. In 2002, approx. 20,500 plasma/tissue samples require drug analysis support for Phase I & III studies. Remaining "other" drug safety costs are Drug Metabolism \$302M. These support remaining studies /documentation required for the NDA.

**Other Support Costs :**

"Other" costs include Discovery Structural Chemistry and Pharmacogenetics \$ 635M with activities planned to evaluate genetic differences of Japanese vs western subjects in Phase I /III studies. Microbiology research \$ 2,166M required support for Phase III micro labs isolate testing, Phase III analysis of clinical resistant isolates and remaining micro studies required for NDA.

What is our approach for microbiology grants? We have set aside \$ 2MM. What are we supporting? Who is deciding what to support? What end are we trying to achieve? How many people do we support and what are we paying on a typical grant? What are we doing with the data?

The external study grants are planned to support label claims, NDA requirements and key ABT 773 communications. Studies range in cost from \$ 5,000 to \$200,000 with the average cost at approx. \$30,000. Study designs are in vitro activity, animal PD models, or a combination of both, and post-approval will also manage investigator -run human studies. An External study committee consisting of Venture, Microbiology, New Product development, AI business development and the Franchise Medical liaison (ML) group meets each month to evaluate submitted proposals. Proposals are approved based on the rationale and expected results in support of the ABT 773 filing and marketing strategy. The committee also develops requests to be sent out to Abbott MLs and ex-US Abbott contacts for specific proposals to support label claims, NDA requirements, or key 773 communication plans. Opinion leaders from every region worldwide are being developed to support global filing and marketing activities.

All external studies are submitted, approved, managed and tracked via the ABT 773 Study Tracking website accessed by the Steering committee and all Abbott MLs (with ex-US Abbott contacts planned to access the website by the end of 4Q 2001). All payments and drug shipments for these studies are also managed via this web -site by Venture document specialists. All approved studies are indexed by study content for searching /reporting capabilities. A web-page containing the draft label will be linked to each of the studies used to support the individual label claims. Multi-center studies will also have the appropriate links to the label claims.

I need more detail on venture management> What are we getting for our \$ 6.7MM? how many heads? What is the approach to travel? What money is squirreled away here? Please take me through it because I need to have a sense of what are the soft spots. For the dept. I have worked on 58 heads, but discounted a full 3 salaries to account unfills during the year. Of these 42 are in 773 and 14 in 492. For travel it is zero based and divided it into 3 parts. (1. Dept including some support area travel to congresses, meetings etc, 2. 492 study travel and 3. 773 study travel). I am working on an easy to justify slide because the assumptions used in 773 and 492 were similar, but I cut 773 budget more than 492 given the size of it. Overall however there is little if any fat in this budget since with the exception of headcount and travel, most other accounts in departmental budget have been reduced.

Our RA/QA budget equals \$ 1.3MM. At \$0.15MM/head, we will have 8 FTEs. Do we really have 8FTEs? Remember, an FTE is a Full time equivalent. I doubt that we have more than 1 RA FTE and there is no way that there are 7 QA FTEs on this project.

The cost represents 4.83FTE for a cost of \$ 1064.9MM in ToxQA, Clinical compliance, Records and PPD RegAffairs. I have reviewed it from a zero base and it seems very reasonable. ( see 492 answer for more detail )

What does HPD IV development mean? What does this consist of? How do we pay them?



ABT-773 IV 2002 Plan.rtf

HPD costs will be charged through inter-divisional services purchased.

On the page called "Phase III Clinical Plan," it is helpful if you denote somehow those studies already underway.  
Will do so.

Your Japanese development plan flow chart is very helpful.  
Great, it exercised my powerpoint skills considerably!

Please add a page summarizing the QT situation (background and required studies).



773 QT issues summary.doc

What can you do this year on the IV program if additional funding is made available, especially for external expenses?

Unfortunately nothing clinically, as we await the first in man trial to begin and data to be generated before we proceed with further studies. From a formulation point of view....

I am confused by what you show for the PK data in the IV program. What is this data and when (how) was it obtained?

I will label more precisely. The PK data shown on the IV slide is a simulation model based on modelling assuming an absolute bioavailability of 35% and linearity of dose response.

Please add a few words describing the likely IV trail that you intend to do - days therapy and how to step down.

The IV trials consist of the following:

Single rising dose (first in man) followed by a multiple dose study for the phase 1 program. The definitive phase 3 trial proposed (subject to regulatory buy in) is a comparative trial of IV ABT 773 followed by oral ABT 773 against IV ceftriaxone with or without IV erythromycin followed by an oral cephalosporin with or without oral macrolide. The subjects would receive initially IV regimen ranging from a minimum of 3 days to max of 7 days followed by an option to change to the oral regimen for the balance of the treatment; which may range from 3 to 7 days. A total of 750 subjects are anticipated for this kind of study. At present it is unclear whether one global trial would satisfy both EU and FDA requirements or separate US and EU trials will be required.

Please add a few words to the Peds slide on what we believe compliance with the FDA's pediatric



program consists of. (p33 or 115) 773 Pediatric program issues.p

I cannot tell from the slides what is the status of the Ped formulation. Have we selected one? If not, what are we looking for and how are we looking for it?

We have no formulation yet. Two prototypes were not bioequivalent to tabs. Taste testing was done on these and it was better than Clari, but worse than Azi. Following our discussions I have determined that we can start the formulation work in Mid OCT, the purpose is to optimise the granules and the suspension. SWix months later we plan to do the 1st clinical bio study.



Please provide GANT charts for the PEDs and IV programs . IV programant chart.pp

ABT-492 Attached is a powerpt presentation for budget backup (6 slides)



ABT-492 cost backup.ppt

see PLAN summary page:

My comments from 773 with respect to CMC andTox also apply here .

CMC support represents 500kg of bulk and formulation development of commerical product . More detail of the breakdown of cost are in attached presentation slide 2. A list of Tox studies and cost are on slide 3. These studies are listed in the current IND submitted to the FDA .

The "other" category here is \$ 4.6MM. The ration to the total program is 4.6/43.4, or > 10%!  
The sheets are new to us all and where to put "other" cost is confusing . The Other cost is Drug Safety should be \$ 1.2MM which represents FTE in Drug Analysis needed to support all PK samples being taken in the Phase I and II studies . (see slide 3)  
Other cost in Support is \$ 2.5MM. Of this \$ 2.2MM represents FTE in the Micro (Discovery) area supporting the evaluation of samples in the clinical trials . See slide 4

Please add a few words to describe the milestone payments .

See slide 6

My questions for RA /QA continue here . The total is nearly the same as 773 yet the clinical activity is a fraction of 773. Something is not correct . Have you challenged the QA people to state their auditing program? Do you agree with it?

The cost represents 4.5FTE in RQA, Compliance, Records and RA .and is zero based . There was 1 mistake of 0.06 being entered in 1 area for 1 study instead of 0.006. ie net result is that 492 is over budgeted by 0.5 FTE in R44J. We have not made any changes at this time . There is a mix difference between the 2 compounds.

ABT-773 G0-202.170			ABT-492 G0-233.270		
	FTEs	\$(000)		FTEs	\$(000)
R42I	1.0	\$ 196.7		0.75	\$ 147.6
R49I	1.0	226.7		0.50	113.3
R44F	0.46	104.3		2.13	482.8
R44J	2.37	537.2		1.68	380.8
Total	4.83	\$ 1064.9		4.31	\$ 1124.5

Once again, for venture management, how many people are we supporting? What else is in here, especially for travel .

2001 support was budgeted for 5 FTE (Ops Mgr, MD, CPM and 2 CRAs). With increase of Phase I and II trials support will increase to 13 (add include 3 CRAs, 2 Doc Clerk, 2 Med. Reviewers and a CPM transferred from 773).

How do travel costs when normalized compare to 773? You could look at it by \$ /patient, \$ /site, or similar approaches . Either way I would like to know what we are doing .

Travel driven by actual number of sites visits for ABT -492

Same micro studies comments as for 773.

*Subsequent pages*



Please lay out the milestone payments . A good place to do it might be on the GANT chart describing the overall program .  
see slide 6

I agree that the LFT map is provocative . Can we provide something similar for Clari for comparison's sake?

Unfortunately that data would have to be looked for in the databases, so there is a longish lead time on that .

Do you really believe that we are getting enough resolution on the AECB Phase II safety study? I think the confidence bounds are very wide .

For two-sided 95% confidence intervals with 80 subjects we have the following for the AECB protocol

Rate	CI
10%	(3.4%, 16.6%)
15%	(7.2%, 22.8%)
20%	(11.2%, 28.8%)
25%	(15.5%, 34.5%)
30%	(20.0%, 40.0%)

Note that levofloxacin clinical trial rates of nausea and diarrhea are 7.1% and 5.6%. Therefore, if we observe a 492 rate between 10-15% in the AECB trial for either of these events, it is likely 492 is worse than levo as the lower end of our 95% CI is 7.2% for an observed rate of 15% (even though CIs would likely overlap between 492/levo within the trial even in this case - levo is acting as an internal control to be sure it performs similarly in our study compared to quoted rates).

If the observed AE rates are less than 10% for 492, then we need to look at 75% and 50% CIs and balance risk of uncertainty vs. commercial implications of potential rate of diarrhea shown by upper bound of confidence interval. For example, 75% and 50% CIs around an observed rate of 10% are (6.1%, 13.9%) and (7.7%, 12.3%), respectively. That means that we are 75% sure that our diarrhea rate could be as high as 13.9% and is at least 6.1% and there is an even chance that it could be as high as 12.3%. Adding an additional 20 patients/arm (n=80) total for study did little to significantly tighten these intervals. It comes down to a balance between cost, time to enroll, and precision of our estimates

Are we really pursuing prostatitis as an indication? (see p.135 for "Continuing Phase I /2a Indications ). Not at present - no phase II studies are being planned - it is merely for safety surveillance .

With respect to the prostatitis work, a picture will be helpful to describe exactly what we think we are investigating . I favor some kind of a distribution curve that indicates the proportion of the population likely to take drug for the duration in the study and then another curve for the proportion of the patient population likely to be exposed at these doses . In other words, I want to illustrate how representative (or unrepresentative ) the data will be of what patients will actually receive .

The purpose of the prostatitis trial is to stress the drug with exposure and duration higher than what we expect to see at registrational levels . For example, we do not plan to go beyond 10 days in our planned indications, so no one should get the drug for 28 days except off label, for which it is not possible to predict usage . With regard to exposure, note that a 600 mg dose provides a mean AUC of 25000 ng\*h/mL. The highest value observed in phase 1 for any subject receiving 100, 200, or 400 mg was only 22000 ng\*h/mL, so our AUCs are above what we would expect even at our highest potential clinical dose . However, that is not to say that an elderly patient or one with reduced renal function would not reach these levels, so the 600 mg dose may be acting as a surrogate for exposures for those at risk populations .

The question we need to be able to answer is what signal would lead us to stop development in this noncomparative trial . Note trova had 9% ALT > 3x ULN in their similar prostatitis study . I seem to recall from an FDA presentation that less than 1% of subjects normally have elevations to this level in placebo controlled trials, although I would need to confirm it . The fundamental assumption behind running this study is that our desire for an ultraclean profile is so high that we would stop development if anything questionable was seen here . If this is not our strategy, we should not do the trial as we will have to live with the consequences .

The slides of the various quinolone uses is not readable in black and white .  
Slides on quinolone use have been updated for easier reading in black and white .  
Stan Bukofzer

The pie charts are provocative, but potentially misleading . You should indicate the launch dates for the various drugs . Is the distribution of the uses a reflection of how drugs grow on the marketplace, how they were originally launched, or something else? I would include the total sales with the pie charts .

Changes made on the chart per your request . Distribution of use has shifted since the introduction of gati (Tequin) and moxi (Avelx) in 2000. These drugs have targeted the RTI indications and captured some share from macrolides .

Need more information on the comment about losing a year during the phase 2b program . I do not understand the comment .

For regulatory status, pls add a few words about the contraceptive issues .



I will . Herewith more detail FYI . ABT-492 OC IND update.pr

The program cost page (p 151) is incomplete .  
Will be corrected

Thanks,


J

John M. Leonard, M.D.  
Vice President  
Global Pharmaceutical Drug Development  
Global Pharmaceutical Research and Development  
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**DB**

Calendar Entry

**Meeting**
☐ Notify me 
☐ Mark Private ☐ Pencil It

Subject		ABT-594 Power Calculations w/Silber, Morris, Leonard/Meel John's AP9 office		Chair		Grace C. Dunn/LAKE/PPRD/ABBOTT	
When	Start	Mon 12/11/2000	02:00 PM	30 mins	Where	Location	
	End	Mon 12/11/2000	02:30 PM			Organizer	
Invites	Required (to)	John M. Leonard/LAKE/PPRD/ABBOTT, David D. Morris/LAKE/PPRD/ABBOTT, Christopher J. Silber/LAKE/PPRD/ABBOTT					
	Optional (cc)	Ericka B. Moore/LAKE/PPRD/ABBOTT, Nancy M. Palbicke/LAKE/PPRD/ABBOTT					
Description							
Your Notes							

**DF**

John M  
Leonard/LAKE/PPRD/ABBO  
TT  
Sent by: Vickie J Enders  
10/05/2001 03:53 PM

Eugene X Sun/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H  
Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, Perry D  
Nisen/LAKE/PPRD/ABBOTT@ABBOTT, Bruce  
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Christopher J  
Silber/LAKE/PPRD/ABBOTT@ABBOTT, Thomas J  
Valente/LAKE/PPRD/ABBOTT@ABBOTT, Stan  
Bukofzer/LAKE/AI/ABBOTT@ABBOTT, TOHRU  
HIROSE/KNOLL/BASF-JAPAN/BASF@BASF-JAPAN@KN  
OLL-AG, Tohru Hirose/OSAKA/AI/ABBOTT@ABBOTT, Jeff  
Drajesk/LAKE/PPRD/ABBOTT@ABBOTT, Laurel A  
Krause-Hooyman/LAKE/PPRD/ABBOTT@ABBOTT, Robert  
C Harris/LAKE/PPRD/ABBOTT@ABBOTT, Amy E  
Potthoff/LAKE/PPRD/ABBOTT@ABBOTT, Carol  
Olson/LAKE/PPRD/ABBOTT@ABBOTT, Hector D  
Yannicelli/LAKE/PPD/ABBOTT@ABBOTT, Anthony J  
Japour/LAKE/PPRD/ABBOTT@ABBOTT, Carol S  
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Kay D  
Kreutzer/LAKE/PPRD/ABBOTT@ABBOTT, Greg T  
Lenz/LAKE/PPRD/ABBOTT@ABBOTT, Michael K  
Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Beatrice  
Rendenbach-Mueller/KNOLL-AG/BASF@KNOLL-AG,  
Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A  
Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Udo  
Legler/KNOLL-AG/BASF@KNOLL-AG, Reinhold  
Janocha/WORCESTER/GPRD/ABBOTT@ABBOTT, Clive E  
Spiegler/PARSIPPANY/GPRD/ABBOTT@ABBOTT, Jessie  
R Groothuis/LAKE/AI/ABBOTT@ABBOTT, Cheryl L  
Renz/LAKE/PPRD/ABBOTT@ABBOTT, Robert J  
Padley/LAKE/PPRD/ABBOTT@ABBOTT, Eddie  
Chong/KNOLL-UK/BASF@KNOLL-UK, Eilis M  
Purcell/LAKE/AI/ABBOTT@ABBOTT, Rainer  
Munschauer/KNOLL-AG/BASF@KNOLL-AG, Bruno  
Schuler/KNOLL-AG/BASF@KNOLL-AG, Lothar  
Daum/KNOLL-AG/BASF@KNOLL-AG, Frank  
Misselwitz/KNOLL-GMBH/BASF@KNOLL-AG, Vaseem  
Iltekhhar/LAKE/PPRD/ABBOTT@ABBOTT, Attila  
Pethoe-Schramm/KNOLL-AG/BASF@KNOLL-AG, Bob  
Barrett/KNOLL-UK/BASF@KNOLL-UK  
Richard G Granneman/LAKE/PPRD/ABBOTT@ABBOTT,  
Reid Patterson/LAKE/PPRD/ABBOTT@ABBOTT, Friedrich  
Richter/KNOLL-AG/BASF@KNOLL-AG, Efraim  
Shek/LAKE/PPRD/ABBOTT@ABBOTT, Steffen  
Roellinger/KNOLL-AG/BASF@KNOLL-AG, Bryan A  
Ford/LAKE/AI/ABBOTT@ABBOTT, Ed  
Ogunro/HPD/Abbott@Exchange@ABBOTT, Gillian  
Hodkinson/LAKE/PPRD/ABBOTT@ABBOTT, Elizabeth  
Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J  
Lynch/LAKE/PPRD/ABBOTT@ABBOTT, Keith F  
Hendricks/LAKE/AI/ABBOTT@ABBOTT, Steve C  
Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, John N  
Simons/LAKE/PPRD/ABBOTT@ABBOTT, Chris G  
Turner/LAKE/PPRD/ABBOTT@ABBOTT, Shakil  
cc Akhter/OSAKA/AI/ABBOTT@ABBOTT, Karen E  
Kerls/LAKE/PPRD/ABBOTT@ABBOTT, Steve  
Szostak/LAKE/PPRD/ABBOTT@ABBOTT, Kay  
Rekau/LAKE/PPRD/ABBOTT@ABBOTT, Amit A  
Sheth/LAKE/PPRD/ABBOTT@ABBOTT, William A  
Brown/LAKE/PPRD/ABBOTT@ABBOTT, Thomas J  
Lyons/LAKE/PPRD/ABBOTT@ABBOTT, Jennifer  
Dart/LAKE/PPRD/ABBOTT@ABBOTT, Karen

Session/LAKE/CAPD/ABBOTT@ABBOTT, Thomas E  
 Woidat/LAKE/PPRD/ABBOTT@ABBOTT, Jeffrey L  
 Meeks/PARSIPPANY/GPRD/ABBOTT@ABBOTT, Olaf  
 Lischke/KNOLL-AG/BASF@KNOLL-AG, Margo E  
 Chiozzi/LAKE/PPRD/ABBOTT@ABBOTT, Kenneth D  
 Stiles/LAKE/PPRD/ABBOTT@ABBOTT, Kathy A  
 Hundley/LAKE/CORP/ABBOTT@ABBOTT

bcc

Subject New Agenda for Monday's PEC Meeting

**GPRD  
 10/08/01 Project Review  
 Agenda**

<u>Start</u>	<u>End</u>	<u>Topic</u>	<u>Presenter</u>
8:00	8:30	Introduction and General Overview	Tom Lyons
8:30	9:15	Portfolio Analysis Overview of PPD/A.I. Projects	Keith Hendricks
9:15	9:25	HSR 903 Patent Issues	Jim Tyree
		<u>Review Development Projects:</u>	
9:25	9:40	J695	Reinhold Janocha
9:40	10:00	D2E7	Clive Spiegler
10:00	10:15	963	Bruce McCarthy
10:15	10:25	201640	Bruce McCarthy
10:25	10:40	Break	
10:40	10:50	ABT 594	Bruce McCarthy
10:50	11:00	KCO	Margaret Foley
11:00	11:15	Segard	Eugene Sun
11:15	11:30	Synthroid	Mason/Chiozzi/Sun
11:30	12:30	General / Working Lunch	
12:30	2:30	Review Phase IV Projects	Margo Chiozzi
2:30	3:00	Portfolio Analysis Overview HPD Pharma Projects	Keith Hendricks
3:00	3:15	Break	
3:15	5:00	Review HPD Pharma Projects	Ed Ogunro
5:00	6:00	Discuss Potential Trade Offs	PEC



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**DG**

Margo E  
Chiozzi/LAKE/PPRD/ABBOTT  
T  
10/05/2001 09:24 AM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Jeff  
Drajesk/LAKE/PPRD/ABBOTT@ABBOTT  
cc Richard J Marasco/LAKE/PPD/ABBOTT@ABBOTT, Heather  
L Mason/LAKE/PPD/ABBOTT@ABBOTT  
bcc  
Subject October 8 program

I have a conference with Jeff and John at 10AM to get clarification of Jeff's plans for Monday.

Chris,  
Will you please take the lead on crafting our role in responding to  
GPRD #7 Where we fit in pain research?  
#8 Synthroid Life Cycle plan  
#11 Who is responsible for Uprima in Japan?

Jeff,  
Please start working on the Depakote phase IV to LRP correlations

I'll call as soon as the conference call ends so we can plan for Monday.

Thanks,  
Margo

----- Forwarded by Margo E Chiozzi/LAKE/PPRD/ABBOTT on 10/05/01 09:14 AM -----

Jeff M Leiden  
10/05/01 07:49 AM

To: Thomas J Lyons/LAKE/PPRD/ABBOTT@ABBOTT, John M  
Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Ed Ogunro  
[HPDAPP00.OGUNREA]@SSWGATE@ABBOTT, Margo E  
Chiozzi/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Richard A Gonzalez/LAKE/CORP/ABBOTT@ABBOTT  
Subject: October 8 program

Rick and I had a chance to review the R and D books (or should I say tomes!)  
Based on that review we would like to suggest the following agenda for the Oct8 meeting

**Introduction and Overview of the budget and comparison to 2001 with emphasis on gaps and issues--Tom Lyons**

**GPRD Programs to be formally presented and reviewed**

1. J695-review phase II program status
2. Segard-why are we spending 9MM when clinical studies are complete and we plan to register in Q2 02
3. D2E7-Please review this program and the PhIV request for \$4.4 MM together-Does this cover other indications, new dosage forms etc
4. HSR-903-Review status of Daichii patent situation
5. Cox-II-Should we develop this for OA, cancer, or Alzheimers-how will this effect next years budget
6. 201640-Please review toxicity data for a go/no go decision
7. Pain program-there are many potentially redundant pain projects for dilaudid and hyrodcodone Please review the entire GPRD HPD pain program together including

Dilaudid  
Rapid dissolve hydrocodone  
controlled release hydrocodone  
Hydrocodone ER/CR  
Dilaudid Oros PhIV  
Vicoprofen Ph IV

8. Review synthroid life cycle management strategy including

T3/T4  
Synthroid Ph IV program

9. KCO-review tox data for a go/no go decision

10. ABT 594-review one additional dosing study

11. Japanese programs

Review dexmetomidine  
uprima  
xemplar

12. Phase IV programs

Gengraf-why are we still spending money on this drug  
Mavik/Tarka-review phase IV program-does this include diabetic nephropathy study  
Norvir-why are we still spending \$1.2 MM  
Depakote-please review ph IV program and tie to financial projections in LRP for the drug  
Please provide a list of additional AI phIV spending programs

13. HPD Programs

Please provide a complete review of rUK program including financial projections for the drug  
Levosimendin-present proposed clinical program and budget  
Clivarine-please present program to get US registration, claims and financial projections  
IV xenon-present program and budget to move this forward  
Drug coated stent-Is this in the HPD budget for 2002  
Zempar programs-review with financial projections  
Next generation iron-review clinical program and progress to date  
Rubitecan-review most recent clinical data-go/no-go decision  
Paclitaxol-please explain incremental spending as drug was just filed  
Precedex ph IV-please review program and financial projections based on incremental spend  
Sevo product improvement-review program

Thanks

Jeff

Jeffrey M. Leiden MD PhD  
Executive Vice President Pharmaceuticals  
Chief Scientific Officer  
Abbott Laboratories  
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100 Abbott Park Rd  
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email: jeff.leiden@abbott.com

**DH**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM: John M. Leonard, M.D.**  
**DEPT: 432, AP9-1**  
**PHONE: 847-938-4545**  
**FAX: 847-937-3918**  
**DATE: October 8, 2001**

TO: Jeff Leiden D-3RD AP6D

CC: Dave Goffredo D-309 AP30  
 Ed Ogunro D-87W AP30  
 Bob Funck D-300 AP30  
 Tom Lyons D-404 AP9  
 Bryan Ford D-4FA AP9  
 Gill Hodgkinson D-477 AP6A

RE: MONTHLY HIGHLIGHTS – SEPTEMBER, 2001

**ANESTHESIA**

Dexmedetomidine

**REDACTED**

**ANTI-INFECTIVE**

ABT-492

- The FDA gave the go ahead to proceed with the biostudy of Phase I vs Phase II formulation, M01-301, as our first US clinical study. This study is targeted to start 10/11. Comments from the FDA have been received on the Phase IIA Acute Bacterial Exacerbations of Chronic Bronchitis study M01-298, and a teleconference with FDA will be held on 10/3.

ABT-773

- The interim analysis for the Phase II Sinusitis QD vs. BID study, M00-225, was completed at the end of September.
- The Phase II Community Acquired Pneumonia QD vs. BID study, M00-219, has currently enrolled 505 of 800 planned patients. An interim analysis will be performed on approximately 500 patients and FDA feedback has been requested on plans to initiate the Phase III comparator trials at 150mg BID.
- Additional pediatric formulation development is being undertaken by PARD to optimize the initial formulations with a target of supplying clinical supplies for a Phase I study in adults by the end of 2Q 2002. A pediatric development timeline is being developed with the key objective of initiating a Phase II study in children prior to the Tablet NDA.

**ANTIVIRAL**

ABT-378/r (Kaletra)

**CARDIOVASCULAR**

Propafenone SR

September 2001 Monthly Highlights  
October 8, 2001  
Page 2 of 3

## **IMMUNOSCIENCE**

D2E7

**REDACTED**

Segard

## **METABOLIC/DIABETES**

Sibutramine - Japan

## **NEUROSCIENCE**

ABT-594

- A modified strategy is in development following program review by the Global Pharmaceutical Executive Committee.

ABT-963

BSF201640

Dilaudid OROS - EU & Canada

## **ONCOLOGY**

ABT-100

- The draft Development Plan/Transition Strategy document was submitted for review on 9/5.

ABT-510 (TSP)

- Notification from FDA was received on 9/27 that the Phase I IND study, M01-302, could proceed.

ABT-627

- The Phase II results and Phase III study designs were presented at CapCure September 7-8.



September 2001 Monthly Highlights  
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Page 3 of 3

ABT-751

- The first two patients started dosing in the Maximally Tolerated Dose study, M00-231, at Vanderbilt on 9/20 and 9/28.

ABT-828

**REDACTED**

**UROLOGY**

ABT-598 (KCO)

**CENTER FOR CLINICAL PHARMACOLOGY AND PHARMACOKINETICS**

**DRUG SAFETY**

**PARD**

**DN**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM:** John M. Leonard, M.D.  
**DEPT:** 432, AP9-1  
**PHONE:** 847-938-4545  
**FAX:** 847 937-3918  
**DATE:** April 27, 2001

**TO:** Jeff Leiden      D-3RD      AP6D

**CC:** Arthur Higgins      D-309      AP30  
Bob Funck      D-404      AP9  
Gill Hodkinson      D-477      AP6A

**RE:** MONTHLY HIGHLIGHTS – APRIL 2001

**ANALGESIA**

ABT-594

The blind was broken on April 23 for M99-114, our Phase IIb Painful Diabetic Neuropathy study, and the results will be available during the week of April 30th.

**ANTI-INFECTIVE**

ABT-492

Based on PK and safety data from the completed Phase I study (Part I-III), we will continue with Phase I and Phase IIA studies planned for 2001.

ABT-773 (Ketolide)

With the ending of the winter season, Phase III enrollment for CAP (224 actual) and sinusitis (278 actual) are behind projections. Phase III start up activities are nearing completion in Central America for CAP and ABS, and in South Africa and South America for CAP for their winter seasons starting in May. Based on slowing enrollment in the northern hemisphere, we have made the decision to proceed with the enrollment.

A strategic decision analysis process has been initiated with the team to evaluate all options for the ABT-773 dose selection, along with its impact on program timing and cost to be presented to management by the end of May.

The initial Phase I study for the IV formulation is being delayed until July to allow for a protocol amendment to further evaluate dose levels and concentration. We also want to evaluate EKG data obtained from the additional pharmacology study in dog requested by FDA. The timing for a Go/No go decision on the IV formulation will be re-assessed once the new start date has been set.

The CMC and Biopharm End of Phase II meeting is scheduled for May 1<sup>st</sup> and will enable us to present our strategy for bulk drug starting materials, our formulation / bioequivalence plans and drug interaction study results and plans.

**ANTI-VIRAL**

Kaletra

The post approval regulatory commitments due 1Q01 to FDA and EMEA have been submitted.

April 2001 Monthly Highlights  
April 27, 2001  
Page 2 of 2

## DIABETES

### ABT-822 (Bimocloamol)

The Phase IIb study unblinding is approaching. Biorex has issued its final pre-unblinding queries, received and entered >80% of the responses, and locked an initial version of the database. Quintiles is performing an audit of this database the week of April 23rd. Pending the results of this audit, final query resolution, final consistency checks, and patient classification, the unblinding is still scheduled for late the week of April 30.

## ONCOLOGY

### ABT-510

Enrollment of first cohort (3 patients at 100 mg continuous subcutaneous infusion) was completed 4/24

### ABT-518

Enrollment of first cohort (3 patients at 24 mg p.o.) was completed 4/23

### ABT-627

With a successful EMEA meeting on 4/23, we are ready to initiate global Phase III pivotal trials in HRPC.

### ABT-751

The U.S. IND was submitted on 4/23.

## PARD

CMC section of IND application for ABT-751 submitted to Reg. Affairs on target.

Apomorphine – support activities leading to launch in EU are on target.

IDC was successfully inspected by MCA on 02 April 2001. Three minor/other observations and two comments were made.

European patent on Modified Release formulation for Clarithromycin successfully upheld. Time has expired for Hexal AG to file for appeal to the opposition decision.

Significant progress was made in understanding the cause-effect relationship for Kaletra SEC dissolution issue. Additional sampling studies revealed some non-uniformity in drug concentration in the lateral direction in the dissolution flask. Based on these results a new sampling plan has been developed. Release testing has resumed utilizing the new sampling plan. New and stability lots are passing mostly at tier 1 level relieving the tightness in the supply chain. In parallel, exploratory studies continue. A pre-approval supplement, coving a tier 2 method to address the need for cross linked capsules, as well as a new tier 1 method proposal, is targeted for filing during 5/01.

**DO**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM:** John M. Leonard, M.D.  
**DEPT:** 432, AP9-1  
**PHONE:** 847-938-4545  
**FAX:** 847 937-3918  
**DATE:** August 10, 2001

**TO:** Jeff Leiden      D-3RD      AP6D

**CC:** Dave Goffredo      D-309      AP30  
Ed Ogunro      D-87W      AP30  
Bob Funck      D-300      AP30  
Tom Lyons      D-404      AP9  
Gill Hodkinson      D-477      AP6A

**RE:** MONTHLY HIGHLIGHTS – JULY 2001

**ANTI-INFECTIVE**

ABT-773

- The Decision Analysis process was completed and presented to senior management on July 25<sup>th</sup>, recommending that the Phase III comparator studies for CAP and ABS be conducted with the 150 mg BID dose. We have reached our target of 500 patients enrolled in the ABS QD vs. BID however, and will have the unblinded results available by the end of September to confirm the BID decision.
- The Phase III CAP and ABS study sizes have been increased to improve the chances of obtaining adequate resistant isolates to support our request for a claim for resistance in the label. Also, based on experience gained from the Ketek FDA advisory, we have increased the size of the safety database. Further confirmation of the adequacy of this database will be pursued with the FDA.
- Based on the above changes to the Phase III program, we are re-assessing timelines to the NDA and anticipate a delay beyond the current target of Aug 2002.
- The Phase I QT study protocol is currently being reviewed at FDA and we anticipate written comments from FDA by mid-August.
- An assessment of the Pediatric development to-date was completed, and a proposal to move forward with further formulation development and Phase I studies has been developed. FDA guidelines for a pediatric formulation require companies to show due diligence with a pediatric development program. A pediatric proposal will be made to senior management.
- The Japan development program is progressing with plans being made to initiate an open label study and a BAL tissue study at the end of 2001. At the completion of the open label study in 2002, a meeting with KIKO is planned to present the Phase III plan and address the potential of a bridging strategy.

July 2001 Monthly Highlights  
August 10, 2001  
Page 2 of 2

## **ANTIVIRAL**

### ABT-378/r (Kaletra)

**REDACTED**

## **ONCOLOGY**

### ABT-627

- The first European Phase III investigator meeting was held July 13-14, and the first three patients were randomized in the M00-244 study.

## **PARD**

## **UROLOGY**

### ABT-598 (KCO)

## **DEXMEDETOMIDINE**

**DQ**



Calendar Entry:

## Meeting

Subject: ABT-773 Presentation to Miles White  
Summarized data and economic and commercial  
implications and recommendations. Location: Executive Conference Room North

Begins: Wed 01/09/2002 02:00 PM Entry type: ☒ Meeting

Ends: Wed 01/09/2002 02:45 PM

Chair: John M Leonard/LAKE/PPRD/ABBOTT

Sent by: Vickie J Enders/LAKE/PPRD/ABBOTT

### Invitations already sent

To: David B Goffredo/LAKE/PPD/ABBOTT@ABBOTT, Eugene X Sun/LAKE/PPRD/ABBOTT@ABBOTT, Jeff M Leiden/LAKE/CORP/ABBOTT@ABBOTT, Miles D White/LAKE/CORP/ABBOTT@ABBOTT, Stan Bukofzer/LAKE/PPRD/ABBOTT@ABBOTT, William G Dempsey/LAKE/Al/ABBOTT@ABBOTT

cc:

- ☐ Pencil In Time will appear free to others
- ☐ Mark Private Others cannot see any details about this event
- ☐ Notify me Have Notes notify you before the event
- Categorize:

Description:

**DR**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM:** John M. Leonard, M.D.  
**DEPT:** R432, AP9-1  
**PHONE:** 847-938-4545  
**FAX:** 847-937-3918  
**DATE:** February 8, 2002

<b>TO:</b> Jeff Leiden	D-03RD	AP6D
<b>CC:</b> Bill Dempsey	D-06WP	AP34
Chuck Fisher	D-0432	AP30
Bryan Ford	D-R4FA	AP9
Bob Funck	D-0300	AP30
Dave Goffredo	D-0309	AP30
Gill Hodgkinson	D-R477	AP6A
Bob Kamen	D-RD22	WO
Suzy Lebold	D-R50A	AP34
Tom Lyons	D-R4R4	AP9
Jill Mueller	D-R4MK	AP6B
Dan Norbeck	D-R473	AP9
Ed Ogunro	D-087W	AP30
Jim Tyree	D-R44I	AP34
Lance Wyatt	D-0390	NC - A1

**RE:** MONTHLY HIGHLIGHTS – JANUARY, 2002

**ANTI-INFECTIVE**

ABT-773

- The Phase I QT Study, M01-325 amendment has been approved and submitted to the IRB. Plans are to restart this study by the end of February.
- The Phase III EU studies for ABECB and ASP have ongoing enrollment. ABECB is targeted to complete enrollment (target 500 pts) by the end of February. ASP enrollment is lagging behind (projected completion, 520 pts by the end of April). The enrollment timeline for ASP will be re-assessed in March.
- The Japan Phase I BAL study has been completed and tissue sample analysis has been started. The Open label study is now enrolling patients (target 50 pts) with a projected completion date of April 02.

**ANTIVIRAL**

ABT-378/r (Kaletra)

- Approval received in New Zealand 24-Jan-02.

**CARDIOVASCULAR**

Propafenone SR

- The major sections of the NDA including Section 3 (Application Summary), Section 4 (CMC), Section 5 (Nonclinical Pharmacology and Toxicology), Section 6 (Human Pharmacokinetics and Bioavailability) and Section 8 (Clinical Data which contains the Medical Reports ISS, ISE, RAFT and ERAFT), are finalized and have been submitted to Regulatory for inclusion into the NDA. The NDA filing date is now projected to be mid March, although this date will depend on the availability of Regulatory resources given the proximity of the D2E7 submission.

January 2002 Monthly Highlights  
February 8, 2002  
Page 2 of 5

- Timelines for preparation of the CPMP package (European Submission) and the target filing date will be established by April.

## **IMMUNOSCIENCE**

### D2E7

- Filing activities continue on track including document sign-offs and peer reviews.
- A proposal for a D2E7 phase IIIb/IV development program was prepared.
- A successful advisory meeting was held in Chicago that provided valuable input toward the Crohn's development program.

### J695

- FDA letters were received for RA, Crohn's and MS and the partial/complete clinical holds were lifted. Women of child-bearing potential can still not be enrolled.
- Abbott received a very positive signal from FDA in a 1/15 telecon that widening of enrollment for the RA program might be feasible. Additionally, the medical reviewer for RA indicated that he would discuss this topic internally. GI/Wyeth received feedback in a 1/18 telecon with FDA that enrollment of women of child-bearing potential might be allowed before Phase III, but not in the currently proposed study IL004.
- Wyeth R&D Council "approved" initiation of Phase IIa study in MS, excluding women of child-bearing potential. Discussions within Wyeth are still needed between Experimental Medicine, Drug Safety, and Head of Wyeth R&D prior to continuation of planning for a proof-of-concept study in psoriasis.

### Segard

- Germany, Sweden, Belgium and Denmark were identified as Abbott's preferred rapporteurs
- A scientific advisory meeting was held on 1/10 with the Belgian authority and they expressed their interest in being a rapporteur.

## **NEUROSCIENCE**

### ABT-089

- Dosing was completed through the 9<sup>th</sup> group in the First Time in Man Single Rising Dose Phase I Study, M00-259, with no significant safety or tolerability issues seen

### ABT-963

- An Advisory Panel meeting was held 1/19, covering COX 2 inhibitor class, OA / RA and Oncology opportunities.

### Dilaudid

- Danish Medicines Authority Clinical Questions were received 1/16.

## **ONCOLOGY**

### ABT-510

- Phase II advisory discussions were held with John Smyth (general) on 1/24 and with Walt Stadler (renal) on 1/25.

### ABT-627

- FDA fast track pre-NDA meeting postponed pending additional responses from agency.
- FDA teleconference requested to discuss a proposed statistical plan for reducing the total enrollment target for the pivotal studies M00-211 and 244.

[FILENAME]

January 2002 Monthly Highlights  
 February 8, 2002  
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#### ABT-751

- Three patients were enrolled in the 200 mg QD dose level. One patient (melanoma) continues at the 300 mg QD dose (fifth cycle).

#### ABT-828

- Technology transfer activities initiated between SPD and ABC on 1/11 and pilot-scale fermentation and isolation runs were initiated in SPD in January.

#### **UROLOGY**

##### ABT-724

- The 2-Week Oral Toxicity study in-life portion completed with no effects seen. Pathology results are expected in mid-February.

##### AU-224 (ABT-224)

- The multiple dose study is planned to begin on 1/19 at the Phase I Unit in Ludwigshafen.
- Process Research have identified process and yield improvement opportunities for bulk manufacture.

##### Sibutramine Japan

- Biweekly video conferencing meeting are being held to discuss and resolve key issues being held between Hokuriku, Eisai and Abbott Park.

#### **CENTER FOR CLINICAL ASSESSMENT**

- Vistas Board decided to consolidate Waukegan operations at St. Therese by early 2005. Meetings will begin in 1Q02 to discuss Vista's financial support of expected \$1.5 MM needed to renovate 6<sup>th</sup> floor of St. Therese into new home for ACPRU. Additional options, beyond the 6<sup>th</sup> floor, being considered.

#### **GPCD (PARD & Drug Safety)**

- The new GPCD organizational structure, including definition and assignment of global and local roles, was rolled out on 1/16/02.
- Key scientific reports on Depakote 250 mg ER were submitted for inclusion in the sNDA filed on 1/31/02.
- Completed manufacture of registration batches for ABT-627.
- Agreement has been reached on PARD projects to be transferred to Ludwigshafen.
- Several key GPCD strategic initiatives were kicked off including the Development Manual, Technology/Science Plan, Key Performance Indicators.

#### **ECO (European Clinical Operations)**

- The clinical trial management system (Fraser Williams Pharma "IMPACT" system) project has been initiated. The kick-off meeting took place on 1/30-31 Ludwigshafen. Representatives from Abbott Park and Ludwigshafen developed a project charter (project description, completion criteria, objectives, risks) for use in ECO and on a global basis. The implementation process as well as tasks, phases and timelines were discussed with FW Pharma. Core Team training at Abbott Park and Ludwigshafen were set for February and the first workshops to define business usage, reference data and system configuration were scheduled for March and April.
- An MS Access database keeping primarily resource information for ECO is under development with release of the first version is planned for March. The database will contain contact information for the affiliates, information on staffing within Europe, project and study information, and resource planning information and will be accessible through the Abbott network.

[FILENAME]

January 2002 Monthly Highlights  
 February 8, 2002  
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- Interviews and recruitment are ongoing in the affiliates. Status will be evaluated in the next ECO-meeting with the affiliates on 2/4 and 2/5.
- The internal postings for Ludwigshafen positions will start in February. Job descriptions of the Country CRA Manager (CCM) as well as templates for an Affiliate Commitment Agreement have been drafted and will be discussed at the next ECO-Affiliate Workshop on 2/4 and 2/5.
- A workshop with venture clinicians and ECO clinical scientists is planned for 2/22 at Abbott Park to finalize the clinical scientist roles and responsibilities in relationship with their US colleagues.
- Discussions with the ventures, MPD and HPD GPRD took place at Abbott Park during the week of 1/15 and studies with potential ECO involvement were identified. This list of about 30 potential studies will be discussed with the affiliate representatives at the next ECO-Affiliate meeting on 2/4 and 2/5 in order to select those studies which match best with ECO's current capacity, the scientific/market interest of the affiliates and the expectations of the clinical sponsors. A final selection will take place during February after venture/sponsor consultation

## R&D OPERATIONS

### Project Services

- 2002 APU: The new web-based planning and budgeting interface (Activity Management and Resource Estimation, or AMARE) has been designed, through the efforts of a cross-functional team from IT, Finance, R&D Operations, Ventures, and several functional areas. System programming is almost complete, and initial training is scheduled for the first week of February.
- The GPRD Project Office has been established, with the hiring and training of the Project Office manager and two Global Project Coordinators. The Project Office has already begun work on the 2002 APU, assisting with the system design and leading the effort to collect the necessary project activity and departmental contact information.
- The GPRD Japan Liaison office has been established, with roles & responsibilities identified in Japan and USA. In January the Liaison office participated in regulatory preparation meetings and advisory panels for ABT-627, Dexmedetomidine, and ABT-963

## GPRD IM&T

### Global Programs<sup>1</sup>

- **AEGIS** – ClinTrace-to-AEGIS conversion was certified Feb. 1 and went live Feb. 3 with migrated Knoll cases; no 483 observations from FDA audit of validation package for AEGIS SHARE (HPD/INET interface and MedWatch-to-AEGIS data conversion) and of AEGIS security; process improvement opportunities identified by team and lessons learned sessions scheduled.
- **CTTS** – Project core team kick-off meeting held Jan 30-31 in Ludwigshafen; first draft of the project charter including deliverables and timelines for the rollout of IMPACT to ECO has been written; key process design workshops have been scheduled at AP and LU.
- **E-Submissions** – Program was restarted this month; RCE is routing for approval; project team leads for Templates, Technology, and Publishing teams have been assigned; business process and functional requirement reviews underway with Venture and Regulatory groups; program master plan will be published in February with weekly status reports of progress vs. plan to follow.
- **IMTS** – Analysis of opportunity to leverage SAP, Manugistics, or Flowstream for clinical supply management indicates that purchasing a specialized package will be lower cost and require less customization; vendor live-test demos scheduled for February; scope expanded per F. Richter to include materials planning and forecasting based on potential to save 20% of clinical supply cost through improved forecasting; cost and time implications to be evaluated.
- **Oracle Clinical** – Main focus of project is development of globally harmonized clinical data management processes supported by standard Oracle Clinical system; analysis of current processes

[FILENAME]

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 February 8, 2002  
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completed for Ludwigshafen and Abbott Park with Parsippany to be completed first week of February; project will kick-off formally in February with videoconference meeting at which John Leonard will address the global project team; next step is harmonized process design estimated to complete in June.

#### Strategic Initiatives

- **D2E7 Submission Support** – Support plan approved by M. Verlinden, M. Roebel, and C. Spiegler; videoconference equipment installed and operational for Regulatory Affairs group in AP30; alternative approach to validating scanning system for CRFs successfully identified and implemented to avoid potential delay producing electronic portion of BLA; secure e-mail connectivity with CBER's pilot program established.
- **CMC IT Strategy** – First draft of CMC IT Strategy delivered to CMC Task Force for review and discussion; critical elements of the strategy include a global CMC LIMS, common stability system, and materials planning and forecasting.
- **Global Collaboration Strategy** – SameTime/Quickplace (real-time document sharing) pilot set to go live Feb. 11 with multiple training sessions to be announced; desktop videoconferencing pilot deferred due to unclear business value; ABC is evaluating use of e-Room for project collaborations.
- **GPRD Planning Systems** – Combined Steering Committee established to oversee AMARE headcount planning system and FMS financial management system to ensure integration and timely delivery; AMARE project charter approved; AMARE on track for training and deployment in February for APU; project team and Essbase development environment established for FMS.
- **Chemical/Biological IS Strategy** – Agreement reached that ABC, LU, and AP Discovery will use TDB as future common biological assay system to replace ELJ/Sprint/Blitz; funding scenarios for deployment at ABC and ALU under review.

[FILENAME]







**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM:** John M. Leonard, M.D.  
**DEPT:** R432, AP9-1  
**PHONE:** 847-938-4545  
**FAX:** 847-937-3918  
**DATE:** April 9, 2002

**TO:** Jeff Leiden                      D-03RD      AP6D

**CC:** Bill Dempsey                      D-06WP      AP34  
Chuck Fisher                      D-0432      AP30  
Bryan Ford                      D-R4FA      AP9  
Bob Funck                      D-0300      AP30  
Dave Goffredo                      D-0309      AP30  
Gill Hodgkinson                      D-R477      AP6A  
Bob Kamen                      D-RD22      WO  
Suzy Lebold                      D-R50A      AP34  
Tom Lyons                      D-R4R4      AP9  
Jill Mueller                      D-R4MK      AP6B  
Dan Norbeck                      D-R473      AP9  
Ed Ogunro                      D-087W      AP30  
Jim Tyree                      D-R44I      AP34  
Lance Wyatt                      D-0390      NC - A1

**RE:** MONTHLY HIGHLIGHTS – March, 2002

**ANTI-INFECTIVE**

ABT-773

- The Phase I QT Study, M01-325 was re-started in March with 28 subjects returning to be screened. The subjects will be completed by the end of April and preliminary results are targeted for early June.
- The Phase III EU ASP study is the only study currently with ongoing enrollment. ASP enrollment is lagging behind with 378 patients (projected completion, 520 pts by the end of April).
- The Japan Phase II Open label study has enrolled 15 patients (target 40 pts). The planned completion date of May 2002 has been extended to Sept 2002 due to the poor respiratory season in Japan.
- The CAP QD vs BID study (M00-219) is undergoing data clean-up and classification currently and the plan is to have this completed by the end of April. Once final issues from classification have been resolved, preliminary results will be available.

ABT-492

- M01-344 CAP trial started in US with 4 patients enrolled in March. Sites in Russia will start next month and Southern Hemisphere sites are targeted to start May through July.
- Protocol has been developed for M01-354 Sinusitis trial and should be submitted to FDA for comments in April.
- The protocol for M01-365 QT assessment study was signed off and will be submitted to the FDA for comments.

**ANTIVIRAL**

ABT-378

- Kaletra Meltrex formulation selected for commercial development.

March 2002 Monthly Highlights  
April 9, 2002  
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## **CARDIOVASCULAR**

### Propafenone SR

- NDA Filed March 15, 2002.

## **IMMUNOSCIENCE**

### D2E7

- The BLA and MAA dossiers have been submitted to the FDA and MAA, respectively.
- All patients have been enrolled into the early EU DCART study, DE013.
- The protocol was approved for the prefilled syringe study, DE043.
- The Juvenile RA study protocol, DE038, was submitted to the FDA.

### J695

- The J695 Development Plan was presented at Abbott Park on March 12, 2002.
- To support the scheduled teleconference on April 10, 2002 with the FDA, a meeting package was submitted on March 20, 2002 which included the proposal that FDA reconsider allowing women of childbearing potential into J695 clinical studies.
- Due to slow enrollment (4 patients in past 5 months), the RA (IL 002) study will be discontinued next month if it has been determined that sufficient PK samples have been obtained from all dose groups.
- In MS, market research has indicated a favorable response to J695, regardless of labeling for pregnancy categorization, if the product offers a beneficial safety and efficacy profile.
- Wyeth had an R&D council meeting on March 26, 2002 where it was confirmed that the MS program will move forward (market research results on MS was presented) and that it would be best if the modified Segment II study in monkeys could be deferred until efficacy has been assessed in one Proof Of Concept study. However, it was recognized that the project is a partnership and that deferral of the modified Segment II and Segment I studies may not be desired by Abbott.

### Segard

- Notification to file submitted to EMEA -- Mar 02
- Meeting was held in LU to discuss Roche manufacturing situation (AI tech ops, new product launch, SPD, ABC, legal).
- CPMP have no objection to either Segard or Tecliar for the trade name for afelimomab.

## **NEUROSCIENCE**

### ABT-089

- Results for the first time in man study (M00-259) have been delayed due to delays in the ECG analysis by the vendor.
- Investigator's Brochure and Protocol for the Multiple Rising Dose Phase I study (M02-411) submitted to the Ethics Committee.

### ABT-963

- Dosing completed in Drug Removal Study (M01-374: Effects of Activated Charcoal and Cholestyramine in the Absorption of ABT-963 in Healthy Subjects). Preliminary results demonstrate a marked increase in clearance (2X) of ABT-963 by activated charcoal when the charcoal is administered starting 24 hours after ABT-963 dosing.

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April 9, 2002  
Page 3 of 10

- Investigator's Brochure and the Protocol for the Multiple Rising Dose Study (M00-250) were submitted to the Ethics Committee.

#### Dilaudid

- Responses submitted to the Danish Medicines Authority for the CMC questions associated with the registration package. (Denmark is the Reference Member State for the EU registration).

### **ONCOLOGY**

#### ABT-100

- Preliminary data from the two-week (with recovery) dog study was reviewed. Recovery of hematological parameters was observed at the lowest dose tested, however further conclusions must await the final pathology reports.

#### ABT-510

- Completed Phase II protocols in renal cancer and NSCLC (3/28).

#### ABT-751

- Study M00-231 (seven-day dosing) three patients continue at the 200 mg QD dose. Three patients enrolled at the 250 mg QD dose, and one patient enrolled at the 125 mg BID dose.
- Site initiation was completed and drug was shipped to the NCI for the pediatric study M01-357.
- Renal cancer protocol was finalized and sent to investigators.

#### ABT-828

- Corporate legal confirmed Pichia expression system licensing agreement with Invitrogen/Research Corporation Technologies allows production of material for preclinical and clinical development.

### **UROLOGY**

#### ABT-724

- PARD has worked with the Venture to establish a liquid formulation and dispensing methodology for the First in Man study (late July '02).

#### ABT-224 (AU-224)

- Multiple-Dose study continues at Phase I Unit in Ludwigshafen. Completed 80-mg dosing with no significant issues or AEs.
- Purkinje fiber studies (canine) results demonstrate that repolarization is not affected at concentrations up to 100 fold therapeutic plasma levels.
- HERG study to be complete in April.
- License Agreement between Abbott and Hokuriku is targeted for sign off in April.

#### Sibutramine - Outcomes

- Continued to revise SCOUT protocol within Abbott (eliminated factorial design and implemented peer review process). Quest Diagnostics selected as central lab and interviews begun with IVRS vendors. Initial drug supply will come from BASF Shreveport
- Responded to update Regulatory Agencies and Affiliates after the Italian Ministry of Health suspended marketing of the drug.

March 2002 Monthly Highlights  
 April 9, 2002  
 Page 4 of 10

### GPCD (PARD & Drug Safety)

- Japanese Ministry of Health and Welfare approved Clivarine vials.
- FDA approved the new tier 1 dissolution method for Kaletra softgel. The same was already approved by the EMEA.
- A Synthroid umbrella PARD team was established to address four different aspects: stability, improved formulation, packaging, and no food effect formulation.
- Received agreement from the FDA on the adequacy of the Zemplar SEC dissolution method and to our approaches to monitoring related substances and SEC moisture content.
- Advanced Parenteral Drug Delivery function transferred to HPD Pharmaceutical Development.
- Selected.

### ECO (European Clinical Operations)

#### Global Projects

**IMPACT** – Due to other commitments of US colleagues (APU, reorganization) the planned IMPACT business workshop could not take place in March, but had to be postponed to a not yet determined later date. Other issues addressed by the Steering Committee were the problem that a harmonized business process to build IMPACT on is not yet existing, that adequate support from senior management is the key business driver for the system and that an internal marketing campaign has to be initiated to prepare future users. It has been agreed upon that due to circumstances phase 1 of IMPACT (roll-out in Europe) will be launched with limited input from the US. The resulting 'European weighted configuration' of the system may need a readjustment once IMPACT will be rolled out to the US. Workshops will be rescheduled and conducted in LU with participation of US colleagues. Presentation of IMPACT at senior staff meetings (John Leonard and Charles J. Fisher) is planned. Through these actions the project should recapture speed and it should be assured that contribution from US business is not a rate limiting step for Phase 1.

#### Strategic Initiatives

**Define roles and responsibilities** - Due to the cancellation of the March trimester meeting the planned attachment of a face-to-face meeting between venture heads, physicians and drug safety representatives to finalize the job description of the European Clinical Scientist could not take place and will be rescheduled at the earliest possibility.

**Identify workload for ECO** - The newly created process to establish a commitment between study sponsor, ECO, and affiliates for ECO performed studies via a respective written agreement has been successfully initiated with the Kaletra QD trial. ECO is awaiting the anti-viral venture's final decision on its cooperation with ECO in this project.

Discussions with study owners about ECO's potential involvement in the conduct of their future studies have revealed that the mission of ECO, its organizational and functional structure are quite unknown to many project managers within ventures and project teams. Next to ECO's own marketing initiatives (e.g. intranet site) support and assistance by senior management is needed to convince study owners of the multiple advantages of working with ECO. Presentation of ECO at senior staff meetings shall help in this process.

A meeting with the affiliate scientific directors and CCMs (country CRA managers) is planned for April 09 and 10, 2002 at Abbott UK to discuss status and process of study recruitment as well as the status of study preparation at the affiliates. At the same time a first presentation the IMPACT system will take place to make the system acquainted to its future users and to get their early buy-in.

#### Glossary of Terms

**ECO** European Clinical Operations. Organization to perform clinical studies in Europe with dedicated, high-quality internal staff for GPRD ventures, HPD and AI/MPD.

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 Page 5 of 10

- ECDC European Clinical Development Center. Clinical Center in Ludwigshafen consisting of Development Projects, European Clinical Operations, Data Management Center Europe, Resource Management and a dotted line to the Therapeutic Area Experts in Europe
- IMPACT Clinical Trial Management System. This system provides a central source for information on overall planning, administration and tracking of clinical trials. At the same time trial unit monitoring and on-site information recording using a portable module is possible. IMPACT will be able to increase transparency, efficiency and focus in trial management, provide trip reports and latest trial overviews from one source. IMPACT is a product of FW Pharma (formerly Frazier Williams). This is a multi-stage project with a pilot phase starting in Germany and The Netherlands this year. Roll-out to other European countries, and then to the US and ROW will follow in a second and third step.

## R&D OPERATIONS

### e-Submissions Business Processes

•

### Project Services

- 2002 APU: Following the March 19th project reviews, the AMARE system was re-opened, project budgets were adjusted, and the system re-locked on March 26th. No significant issues were encountered.
- AMARE user feedback was received via written survey (27 responses) and several user meetings. This feedback will help in the design of the next Planning-Budgeting-Resourcing system ("PBR Phase II").
- The PBR core team has scoped out several options for Phase II. The team will make a recommendation to the Steering Committee on April 5th.
- Lin Lauruson is joined R&D Operations as the Program Manager for Project RAPID. He has begun to organize the candidate RAPID projects for 2002 for prioritization and initiation.
- The Japan Liaison office assisted in the Dex DEC meeting response preparation.





Perry D Nisen  
01/08/2002 08:09 AM

To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
cc:  
Subject: Re: Goodwin Philanthropy

John  
This is a revised version of what I sent you the other day

----- Forwarded by Perry D Nisen/LAKE/PPRD/ABBOTT on 01/08/02 10:09 AM -----



Perry D Nisen  
01/08/02 10:08 AM

To: Jeff M Leiden/LAKE/CORP/ABBOTT@ABBOTT  
cc: William M Dwyer/LAKE/AHD/ABBOTT@ABBOTT  
Subject: Re: Goodwin Philanthropy

Jeff  
Attached is a proposal/presentation to Goodwin. I think it addresses your comments and those of Bill Dwyer. I'll ask Siobhan to make it look nice.



goodwin presentation.p

Perry

Jeff M Leiden

Jeff M Leiden  
12/12/01 07:56 AM

To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: Goodwin Philanthropy

Perry

Thanks for your proposal

See below for my responses  
We should work with Siobhan to put together a nice looking glossy proposal for him

Jeff

Jeffrey M. Leiden MD PhD  
Executive Vice President Pharmaceuticals  
Chief Scientific Officer  
Abbott Laboratories  
Dept 03RD, BLDG AP6D  
100 Abbott Park Rd  
Abbott Park, IL 60064-6020

Phone: 847-938-9313  
Fax: 847-937-2632  
email: jeff.leiden@abbott.com

Highly Confidential

Perry D Nisen



Perry D Nisen

12/11/01 12:11 PM

To: Jeff M Leiden/LAKE/CORP/ABBOTT@ABBOTT

cc:

Subject: Re: Goodwin Philanthropy

If you agree, I will suggest that Goodwin support academic 'Centers of Excellence in Oncology Drug Development' to enable them to conduct phase I and proof of principle studies with Abbott compounds. We can recommend first rate institutions that are also top Abbott customers (e.g. Duke, Northwestern, Hopkins, etc).

I will breakdown the budget for him, but broadly, a Center of Excellence might fund the following headcount:

- data manager (and statistics)
- research coordinator
- Q/A GCP compliance
- project/business manager (to coordinate billing/reimbursement for conventional care vs research)
- medical writing (protocols/summaries/IND reports)

I like this idea

We can restrict the opportunity to molecules that did not pass our prioritization:

ABT-518 (MMPI)

- complete phase I (\$ 2 MM),
- phase II proof of principle in melanoma (\$ 2 MM)

ABT-271 (this is a soluble taxane that was DDC approved, but not developed because of prioritization and intellectual property risk)

- drug supply (\$ 0.4 MM)
- toxicology (\$ 0.6 MM)
- phase 1 (\$2.4 MM)

ABT-578 (DDC approved rapamycin analog, unfunded. Wyeth is developing one for cancer indications)

- drug supply (\$ 0. 5MM)
- toxicology (\$ 0.3 MM)
- phase I (\$1.5 MM)

I would prefer to fund the partially funded and additional studies described below first.

What about compounds that are 'partially' funded or still preclinical?

ABT-963 (cox-2 inhibitor) for chemoprevention

ABT-828 (K5 angiogenesis inhibitor)

ABT-100 (FTI)

What about supporting additional studies for compounds currently in development?

ABT-510 (TSP mimetic angiogenesis inhibitor) (other cancers, non-cancer indications e.g. proliferative retinopathy, arthritis, psoriasis, etc)

ABT-751 (antimitotic) (multiple cancers)

ABT-627 (atrasentan) (additional other cancers)

There are also marketed drugs that have potential oncology application but that we would not fund ourselves:

Zyleuton for chemoprevention

Highly Confidential




Clarithromycin for gastric cancer chemoprevention

On another note, and this is probably none of my business, but spies tell me that Paul Berns is being recruited heavily outside Abbott.

Perry

Perry Nisen MD PhD  
Divisional Vice President  
Global Oncology Development  
GPRD  
Abbott Laboratories  
200 Abbott Park Rd, AP30-3, D-48J  
Abbott Park, IL 60064-6145  
Telephone 847-938-7212, FAX 847-937-8460  
perry.nisen@abbott.com  
Jeff M Leiden

Jeff M Leiden  
11/30/01 03:14 PM

To: William M Dwyer/LAKE/AHD/ABBOTT@ABBOTT  
cc: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT, Kathy A  
Hundley/LAKE/CORP/ABBOTT@ABBOTT  
Subject: Re: Goodwin Philanthropy 

Bill

I suggest that you set up a date for Perry, myself and you to fly down to see Goodwin  
Kathy will help you get the corporate jet and work to give you dates from my calendar that will work

Perry

Can you please put together a specific proposal covering several compounds and trials with a rough budget to present to him during our visit

Thanks  
Jeff

Jeffrey M. Leiden MD PhD  
Executive Vice President Pharmaceuticals  
Chief Scientific Officer  
Abbott Laboratories  
Dept 03RD, BLDG AP6D  
100 Abbott Park Rd  
Abbott Park, IL 60064-6020

Phone: 847-938-9313  
Fax: 847-937-2632  
email: jeff.leiden@abbott.com

Highly Confidential

William M Dwyer

William M Dwyer  
11/30/01 12:42 PM

To: Jeff Leiden  
cc: Sue Widner, Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: Goodwin Philanthropy

Dear Jeff,

I spoke with Bill Goodwin yesterday and he is interested in following up on Perry's idea of funding cancer drug candidates that otherwise aren't supported by available resources. He acknowledged that other companies might have similar business issues, but felt Abbott is in the front of the line as we brought this to their attention. Earlier you indicated that you would probably want to meet one-on-one with Mr. Goodwin in Richmond to pursue this idea. His contact information appears below. It probably makes the most sense to have your office set this up directly. I'll be glad to assist if appropriate.

I also spoke with Northwestern who appear more interested in a direct research contract as opposed to philanthropic funding for this specific example. They have some concern about how a tax free foundation could pass funding to another not-for-profit organization that would result in a benefit to a corporation like ours. They are eager to work with Abbott and would like to be considered as a site if this clinical research (or other) moves forward. Mr. Goodwin would also entertain a proposal to advance cancer research directly from Northwestern. He has visited Mayo, Hopkins and Sloan in addition to the Abbott Park visit. They will also go to M.D. Anderson before he decides finally what to do.

CONTACT INFORMATION:

William H. Goodwin, Jr.  
One James Center  
901 East Cary Street  
Richmond, VA 23219  
ph (804) 643-4200  
Sec. "Sherri"

Best regards,

Bill

Highly Confidential

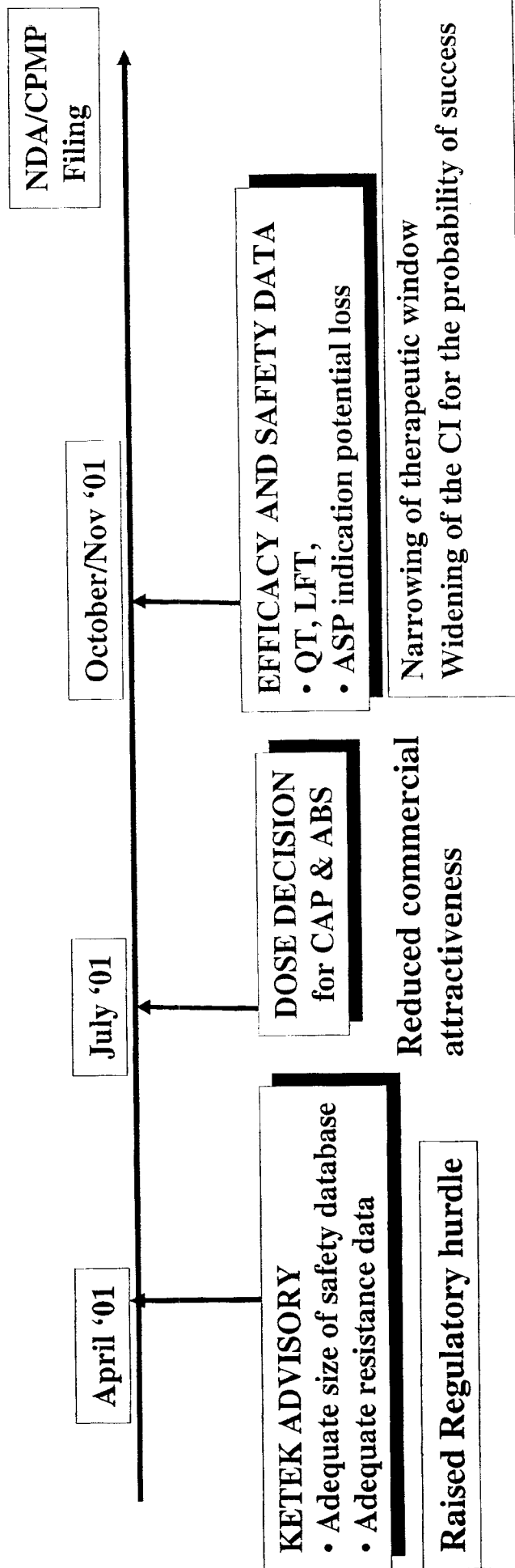
**EC**

# ABT 773 Agenda

- Update on key developments since the last PEC
  - Ketek FDA Advisory Meeting
  - Dose Decision for CAP and Sinusitis
  - Efficacy and Safety Data
- Impact of key developments on product profile and NPV of the program
- Future options for the program

# ABT 773 Team Summary and Recommendations

Since the April PEC, the development plan has been impacted by:



**Summary: Reducing NPV of the product**

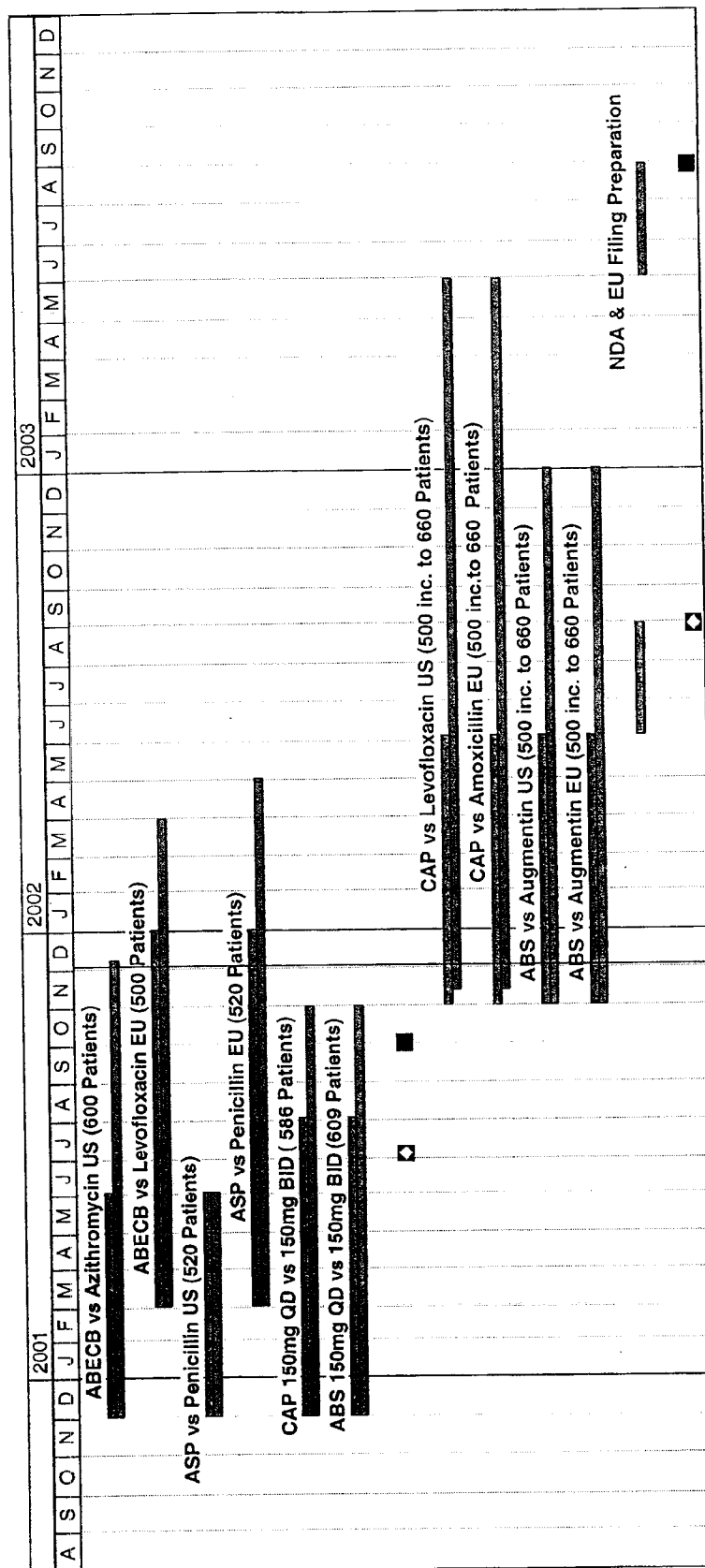
# ABT 773 Target Profile

Target Indications	
Bronchitis	5D QD
Pharyngitis	5D QD
Pneumonia	10D QD/BID
Sinusitis	10D QD/BID

Attribute	ABT 773	Clari	Levo	Azi	Ketek
<b>QD dosing</b>	ABECB/ASP QD CAP/ABS QD/BID	QD	QD	QD No ABS	QD
<b>Short-duration therapy</b>	ABECB/ ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
<b>Resistance Claim</b>	Pursuing	✖	✓ (15/15 isolates)	✖	Pursuing
<b>Safety</b>	QT, liver, CYP3A	QT and liver liabilities, CYP3A	No safety issues	No safety issues	QT /liver, CYP3A

# KETEK advisory emphasized the regulatory hurdles regarding safety and resistance

- Ketek data insufficiently robust to obtain a resistance claim
- Emphasized QTc and liver function concerns for ketolides



Increased Costs to NDA: \$53MM

Increased time to NDA: 1 year

# Capturing the 2001 winter season drives early BID Dose Decision for CAP/Sinusitis

- Assessed six alternative strategies based on technical, regulatory and commercial attributes

Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	ABECB/ASP QD CAP/ABS BID w/QD follow on	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates ( ~1500 CAP pts)	Under exploration	✓ (15/15 isolates) 100%	✗	✗ (14/17 isolates) 82%
Safety	QT, liver Added 1000 pts (to achieve BID database ~3200pts)	Approved	Approved	Approved	US ?20 000 pts due to liver/ QT concern, EU approval



# ABT-773 Phase III Efficacy Data to date

Study	Indication	Comparator	Number ABT-773 Subjects	ABT-773 Dose/ Duration in Days	Status
US, EU (IND) M00-225	Sinusitis	NA	660	150 BID x 10 d 150 QD x 10 d	84-86% interim analysis
US, Canada (IND)	Sinusitis	Augmentin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	Sinusitis	Quinolone	660	150 BID x 10 d	Ready to dose
US (IND) M00-219	CAP	NA	600-800	150 BID x 10 d 150 QD x 10 d	585/600 Unblind Jan
US (IND)	CAP	Levofloxacin	660	150 BID x 10 d	Await FDA
EU (Non-IND)	CAP	Amoxicillin	660	150 BID x 10 d	Ready to dose
US	Pharyngitis	Penicillin	520	150 QD x 5 d	Failed
EU	Pharyngitis	Penicillin	520	150 QD x 5 d	223/520
US	ABECB	Azithromycin	600	150 QD x 5 d	578/600
EU	ABECB	Levofloxacin	500	150 QD x 5 d	327/500

## US: M00-223 (IND study)

### ABT-773 150 mg QD VS Penicillin V 500 mg TID Streptococcal Pharyngitis/Tonsillitis

- Treatment groups :
  - ABT-773 150 mg on Study Days 1-5
  - Penicillin V 500 mg (250 mg x 2) TID tablets on Study Days 1-10
- 2 different protocol designs for Test-of-Cure (TOC) Visits EU vs US

Pen V dosing complete

ABT 773 dosing complete

M00-223 US  
TOC visit

M00-222 EU<sub>7</sub>  
TOC Pen

M00-222 EU  
TOC 773

Days

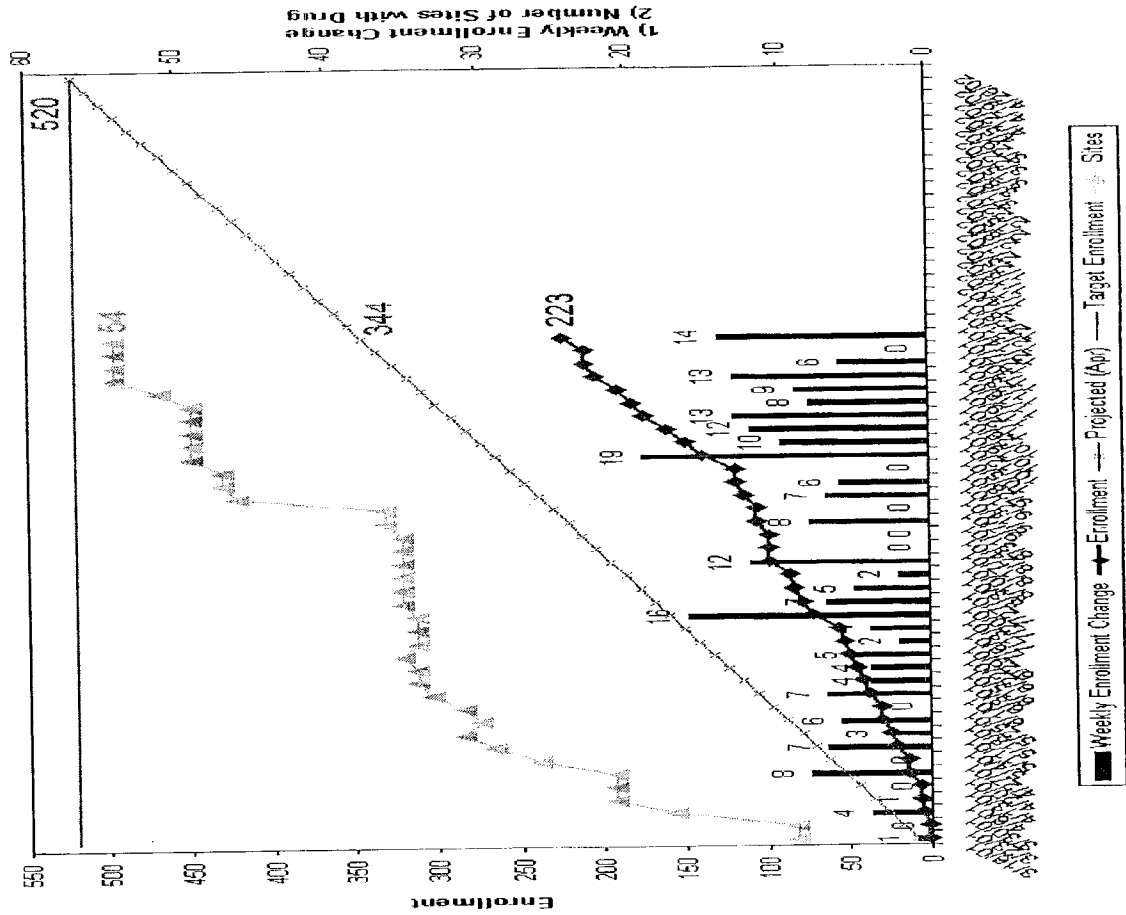
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
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M00-223 US Pharyngitis Study  
Eradication Rate at Test-of-Cure Visit

	ABT-773	Penicillin	95% CI	P-value
<u>Bacteriological</u>				
PP	74% (140/189)	90% (170/189)	(-23.7, -8.0)	<0.001
ITT	64% (141/220)	81% (171/212)	(-25.1, -8.0)	<0.001
<u>Clinical</u>				
PP	85% (160/188)	93% (175/188)		

# Decision that EU ASP Trial continues

**M00-222 ASP Study (Ex-U.S. Sites)**  
**Acute Streptococcal Pharyngitis**



- Indication with 150mg QD lost:
  - **US:** Non-approvable, less than 85% bacteriological cure and less than 10% difference
  - **EU:** Likely non-approvable, less than 10% difference to Penicillin and >80% in 2 trials
- Projected enrollment completed Apr 2002.
- Initial results available Aug 2002.

# **Pharyngitis and earlier Sinusitis Data are Consistent**

- Pharyngitis indication: test of cure is bacteriological  
Sinusitis cure rates 86% BID vs 84% QD based on clinical cure with presumed eradication.
- Indications at different doses;
  - Sinusitis 150 mg QD less effective than 150 mg BID even at 10 days
  - Pharyngitis result findings consistent with clari failure at 5 days and success at 10 days therapy
- Sinusitis had no comparator and will still be tested

## Impact of Pharyngitis Results on Bronchitis Indication at 150mg QD

- Bronchitis trial likely to succeed based on clinical cure rate (blinded clinical rate 82%)
  - Placebo effect
- Bacteriological failure in pharyngitis raises issues of bacteriological efficacy at 150mg QD dose
  - *S. pyogenes* and *S. pneumoniae* have similar MIC profiles
- Bronchitis is only indication left at 150mg QD dose
  - will not be supported by CAP data (occult CAP a clinical concern - EU)





# Impact of pharyngitis data on the product profile

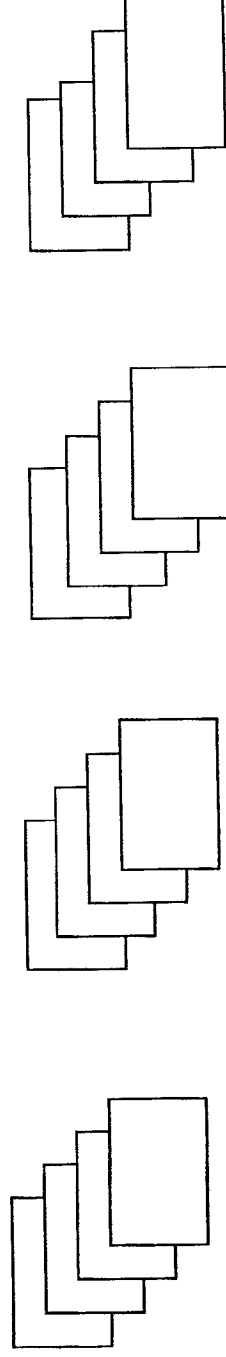
Attribute	ABT 773	Clari	Levo	Azi	Ketek
QD dosing	CAP/ABS BID* ASP QD ✖ ABECB QD?	QD	QD	QD No ABS	QD No ASP US
Short-course therapy	ABECB/ASP 5D CAP/ABS 10D	ABECB/CAP 7D ABS 14D	7-14D	5 D	ABECB/ASP 5D CAP/ABS 7-10D
Efficacy with resistant organisms	Pursuing 15 isolates Increased to 25 isolates ?	Under exploration	✓ (15/15 isolates)	✖	✖ (14/17 isolates)
Safety database	QT, liver Added 1000 patients ?	Approved	Approved	Approved	US ?20 000 pts due to liver/QT concern, EU approval

•\*Possibility of a QD follow on is limited for all indications.

•ASP 10days and /or BID repeat studies thought to be commercially unattractive

# Safety: M01-325 QT Study Design

- 68 Healthy males and females, 20% greater than 50 years old.
- Double-blind, multiple-dose, four-period crossover each period dosing 5 days, 10 day washout
-  Placebo,  150 mg BID,  300 mg BID,  450 mg BID
- Randomized, into 1 of 4 sequences containing



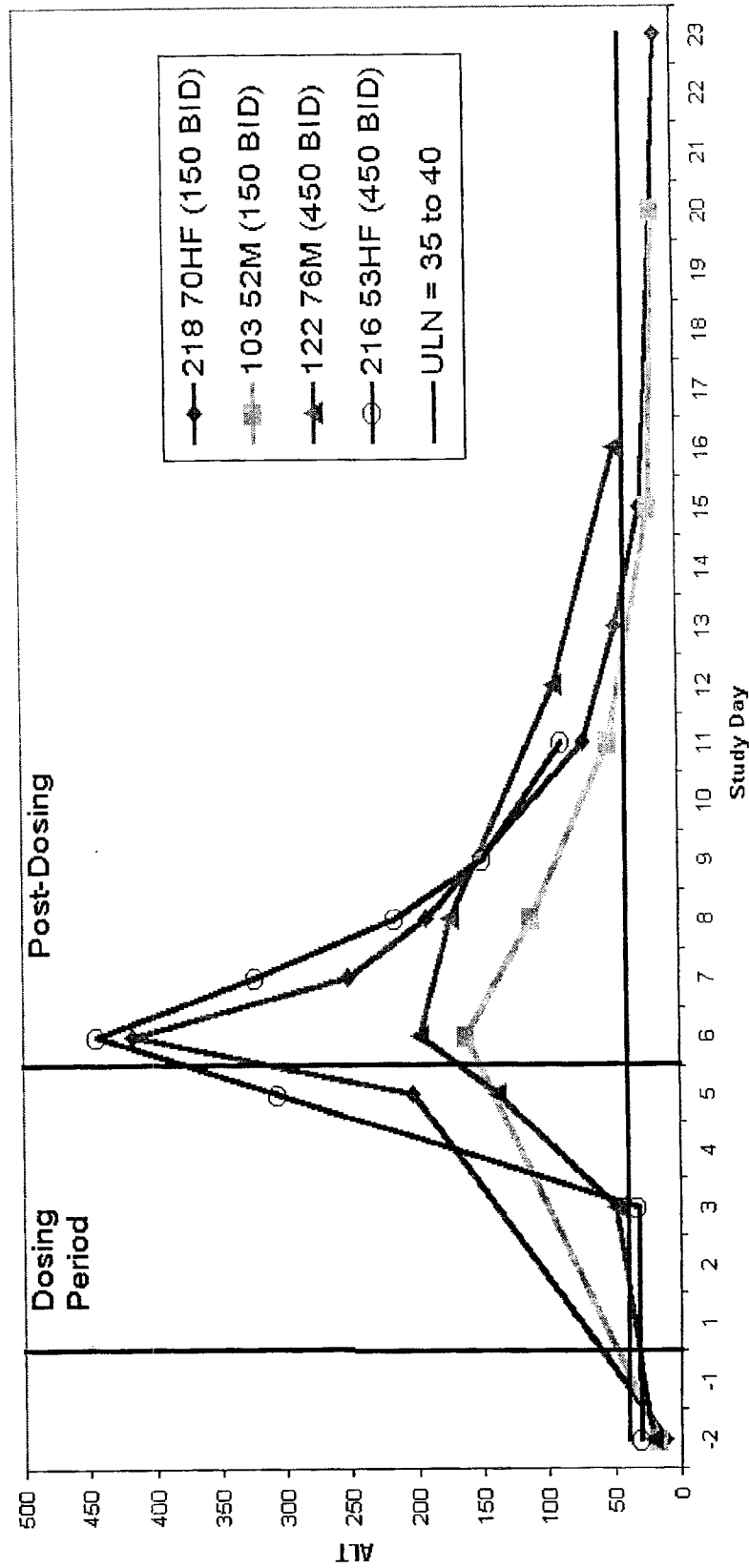
Each period ECG collection:

Day -1 Placebo baseline, Day 1, Day 5 ECG and PK



Study M01-325: 4 Subjects with Significantly Elevated  
( $>3\times\text{ULN}$ ) ALT (All  $>50$  years old)

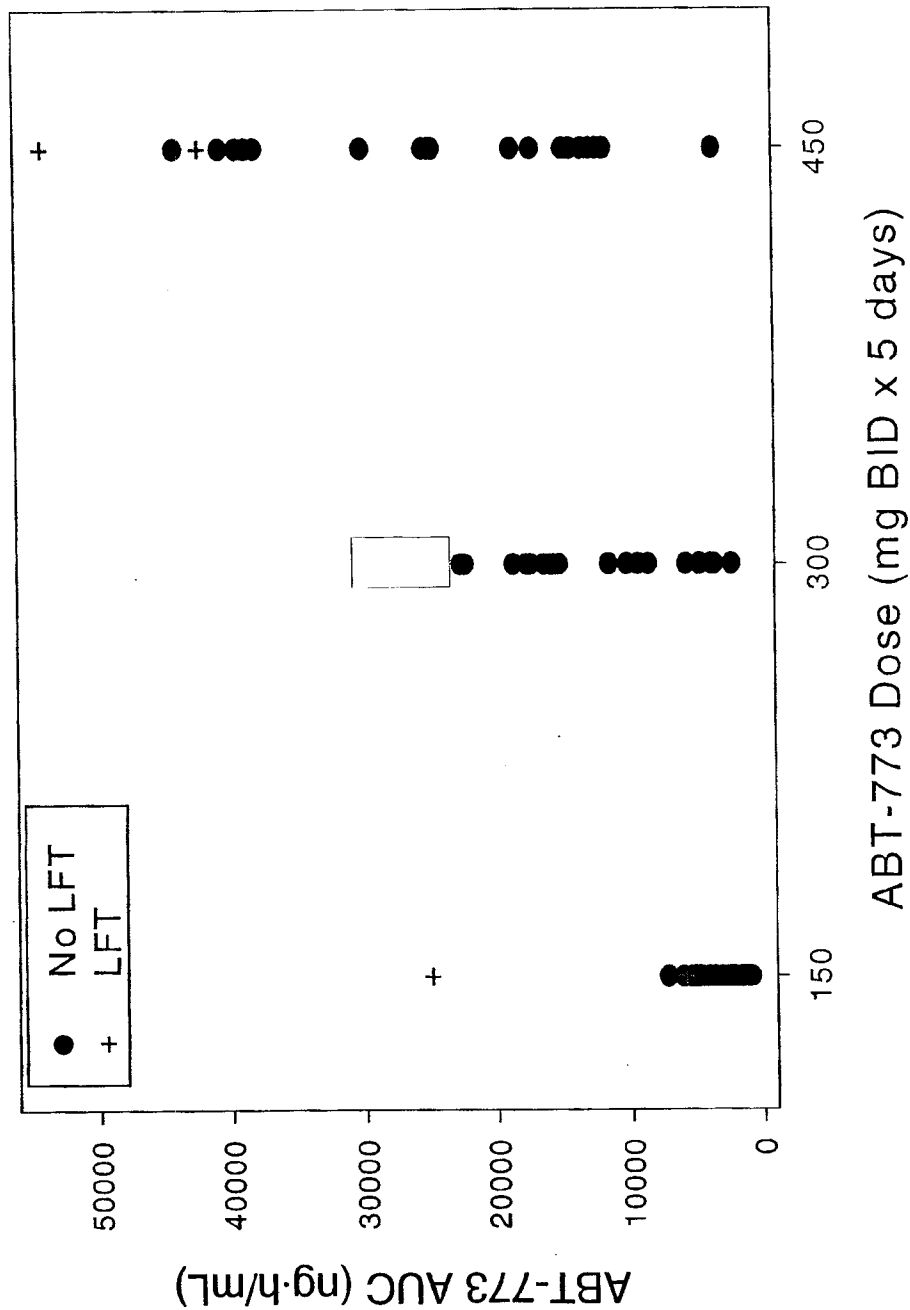
ABT-773, Study M01-325



2 subjects at 150mg BID and 2 subjects at 450mg BID

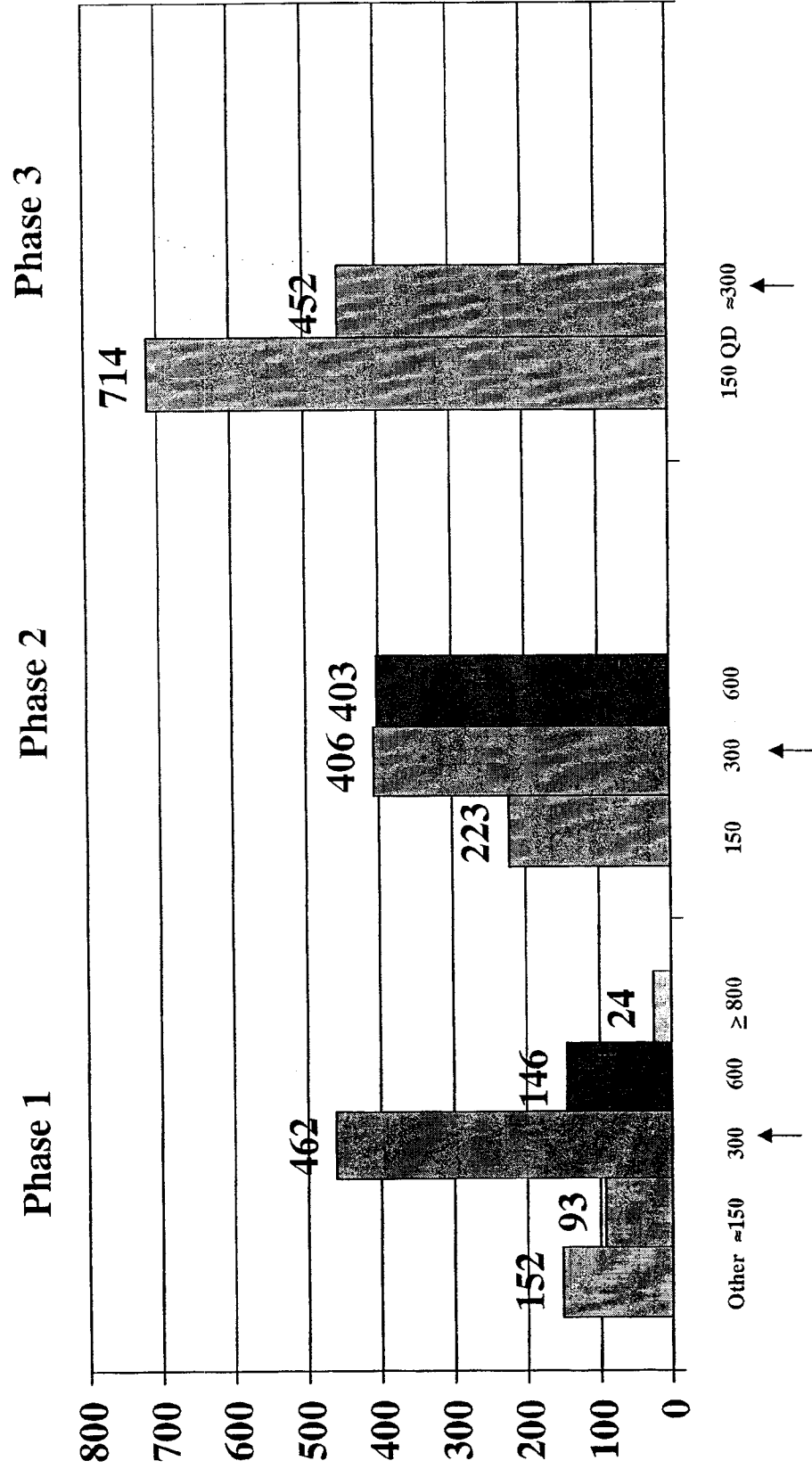
# Study M01-325: Relation Between Dose and Day

## 5 ABT-773 AUC<sub>0-18</sub>



LFT = Subjects 103, 122, 216 and 218; No LFT = All other subjects.

# No. of Subjects Available for Analysis



Other: single dose or blind data

# Overall Incidence of LFT's Not Changed (All Subjects with LFT)

	$\geq 3 \times$ ULN
Original overall N=2884	39 (1.4%) [1.0, 1.8]
New overall N=2939	43 (1.5%) [1.1, 2.0]
Current Phase 3 N=1047	17 (1.6%) [0.9, 2.6]

**Investigation of the Available Database Exhibits Low  
Concern for Continuing at 150mg BID and 300mg BID  
Overall ALT Abnormality Rates in Phase 2 and 3  
(Normal at Baseline -- ALT <1x ULN)**

	> 1x ULN	≥ 2x ULN	≥ 3x ULN	≥ 5x ULN
<b>150 mg QD</b>	71/738 (9.6%) [7.6, 12.0]	8/738 (1.1%) [0.5, 2.1]	3/738 (0.4%) [0.1, 1.2]	2/738 (0.3%) [0, 1.0]
<b>150 mg BID alone</b>	38/344 (11.0%) [7.9, 14.8]	4/344 (1.2%) [0.3, 3]	1/344 (0.3%) [0, 1.6]	0 [0, 0.8]
<b>300 mg daily (includes 150 mg BID)</b>	88/667 (13.2%) [10.7, 16.0]	8/667 (1.2%) [0.5, 2.3]	3/667 (0.4%) [0.1, 1.3]	0 [0, 0.6]
<b>600 mg daily</b>	59/327 (18.0%) [14.0, 22.6]	8/327 (2.4%) [1.1, 4.8]	2/327 (0.6%) [0.1, 2.2]	1/327 (0.3%) [0, 1.7]

- Only 24 patients at doses 800mg or above
- Dose response demonstrated increases at 600 mg

# ALT Changes at Post-Therapy 1-2 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Clari ER* N=783	ABT-773& 150 mg QD N=574	ABT-773@ 150 mg BID N=328	ABT-773 # 300 mg N=633	ABT-773 ^ 600 mg N=314
>1x ULN	35 (4.5)	50 (8.7)	24 (7.3)	55 (8.7)	39 (12.4)
≥ 2x ULN	3 (0.4)	6 (1.0)	3 (0.9)	6 (1.0)	2 (0.6)
≥3x ULN	0	2 (0.3)	1 (0.3)	2 (0.3)	0
≥5x ULN	0	1 (0.2)	0	0	0

\*Clari ER similar to Clari IR and MR

\*Clari ER Phase 3, ABECB, ABS and CAP

&Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

^ Phase 2, including 200mg TID and 600mg QD.

¶ Number (%)

# ALT Changes at Post-Therapy 7-14 Days After Last Dose (Subjects with Normal at Baseline)

ALT Value	Ketek N=1232*	Comparator N=1031*	ABT-773& 150 mg QD N=618	ABT-773@ 150 mg BID N=302	ABT-773 # 300 mg N=598	ABT-773 ^ 600 mg N=273
>1x ULN	98 (8.0)	92 (8.9)	36 (5.8)	23 (7.6)	46 (7.7)	34 (12.5)
≥2x ULN	6 (0.5)	4 (0.4)	2 (0.3)	1 (0.3)	3 (0.5)	4 (1.5)
≥3x ULN	1 (0.1)	3 (0.3)	1 (0.2)	0	1 (0.2)	2 (0.7)
≥5x ULN	0	0	1 (0.2)	0	0	1 (0.4)

\*Ketek Phase 3

&Phase 2 and 3; @Phase 3; #Phase 2 and 3, including 100mg TID, 300mg QD and 150mg BID.

^ Phase 2, including 200mg TID and 600mg QD.

¶ Number (%)

# Maximum ALT Changes in Phase 3 CAP (Ketek, Clari ER, ABT-773)

## Studies in Subjects with Normal Baseline Values

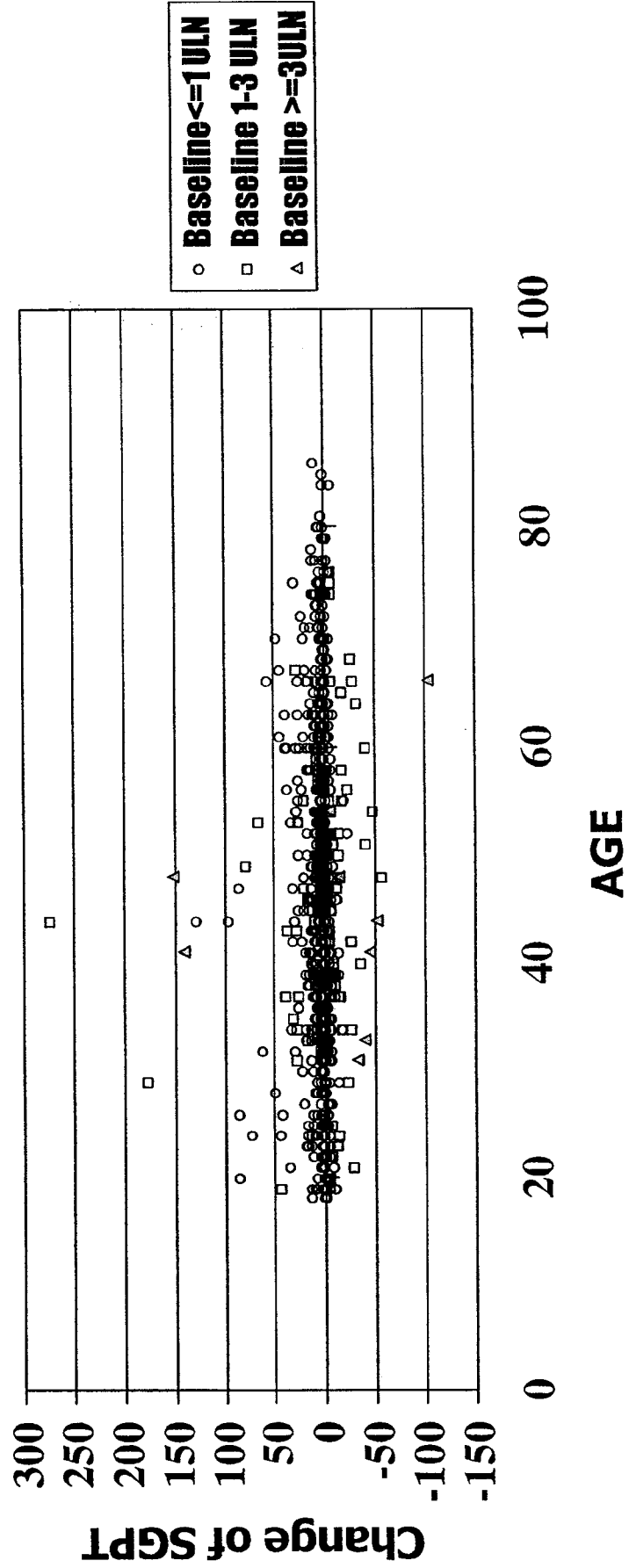
ALT Value	Ketek 800 mg QD N=395	Clari ER* 1000 mg QD N=121	ABT-773 150 mg BID N=148
>1x	86 (21.8)	14 (11.6)	17 (11.5)
≥2x	14 (3.5)	5 (4.1)	2 (1.4)
≥3x	4 (1.1)	0	1 (0.7)
≥5x	1 (0.3)	0	0

\* Clari ER similar to Clari IR and MR



Phase 2/3 (Age Effect)  
Maximum Change from Baseline  
300MG Total Daily Dose

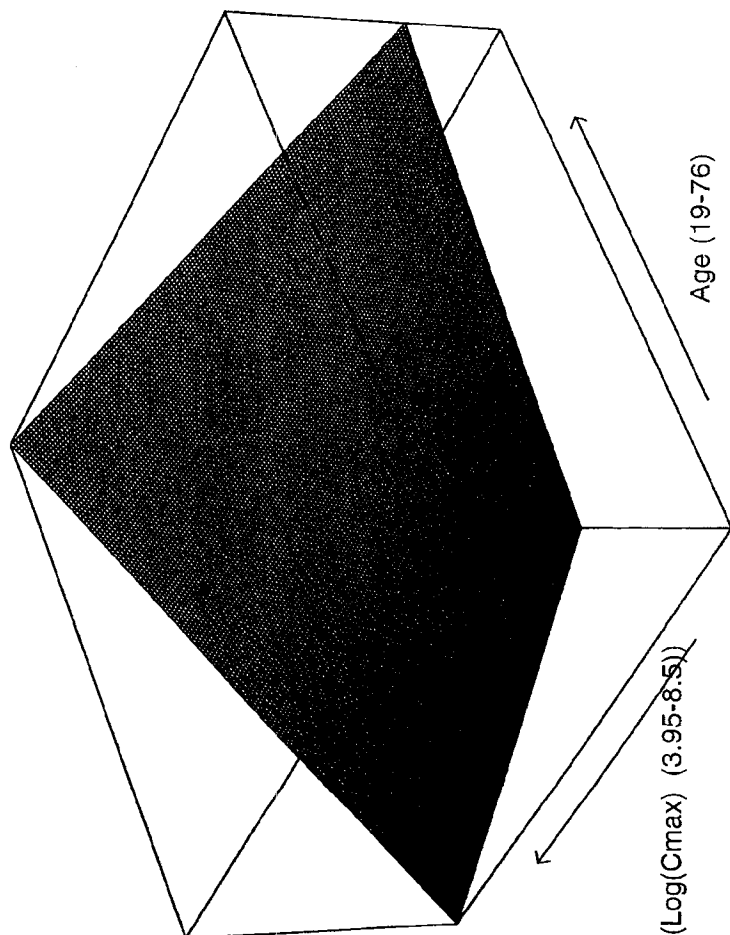
**Change of SGPT vs AGE**



# 3D Model defines relation between hepatotoxicity, dose and age

ABECB 60 yrs  
CAP 50 yrs  
Sinusitis 40 yrs  
Pharyngitis 30 yrs

Log(SGPT)



Studies included:

M97-796  
M99-011  
M99-016  
M99-018  
M99-024  
M01-325  
M98-967

$$\text{Equation: } \text{Log}(\text{SGPT}) = 2.622678 + \text{Log}(\text{Baseline}) * 0.7179079 - 0.05743167 * \text{age} - 0.2609751 * \text{Log}(\text{Cmax}) + 0.009588997 * \text{age} * \text{Log}(\text{Cmax})$$

## No “Index” Case to Date in ABT-773

- Up to 3% 3x ULN LFTs acceptable in antibiotics  
(CDER-PhRMA-AASLD conference Nov 2000)
- Asymptomatic
- Reversible
- No change in bilirubin (Hy’s law)
- No chronicity

Ketek had 2 index cases

This can drive an increased database need.

Quinolones—6,000 patients

“Hy’s law”—10,000 patients

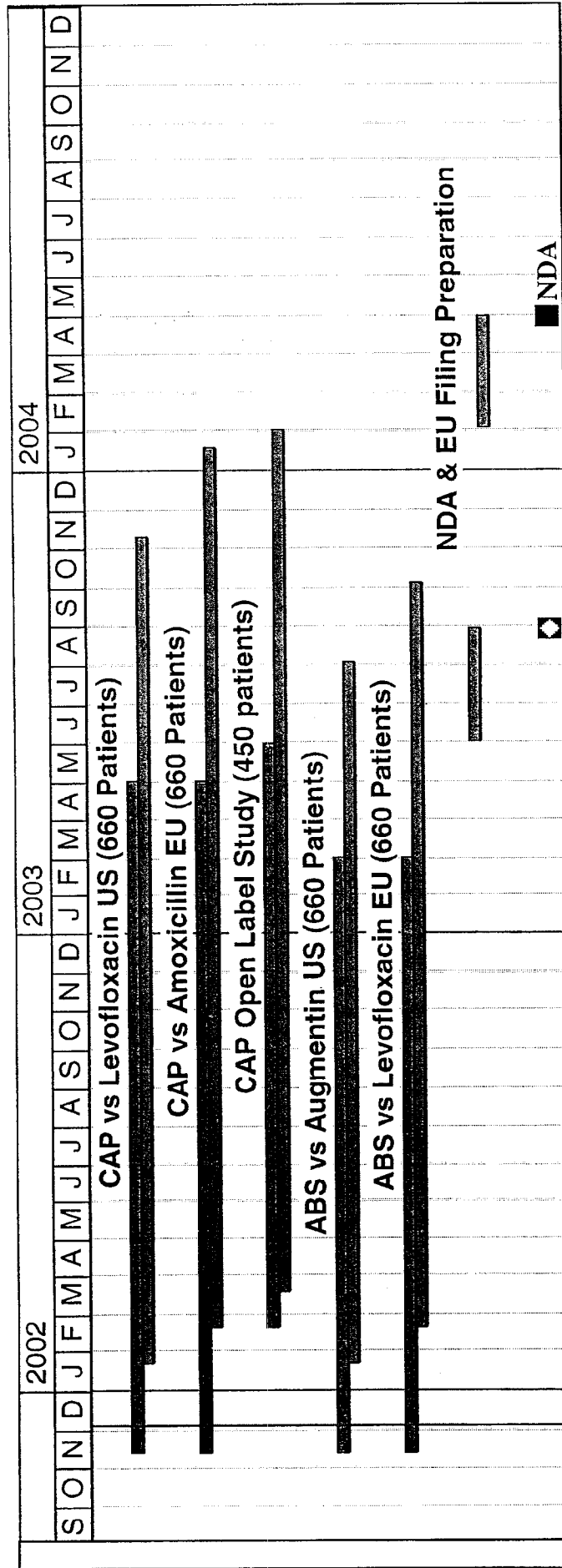
## Conclusions from Complete Analysis of LFTs

- Overall average event rate is relatively unchanged
  - 4 cases in QT study
  - (7 cases in Japanese bridging study)
- Definite drug effect with possible greater risk in older individuals and higher doses.
- No. of patients with  $\geq 3$ x ULN ALT within accepted limits for antibiotics at 150mg BID (includes phase 3 trials) (CDER-PhRMA-AASLD conference Nov 2000)
- No 'index' case to date
- No single clinical identifier of patients at risk, with possible exception of elderly

# Regulatory Implications of LFT Findings on QT Study and Phase 3 Trials

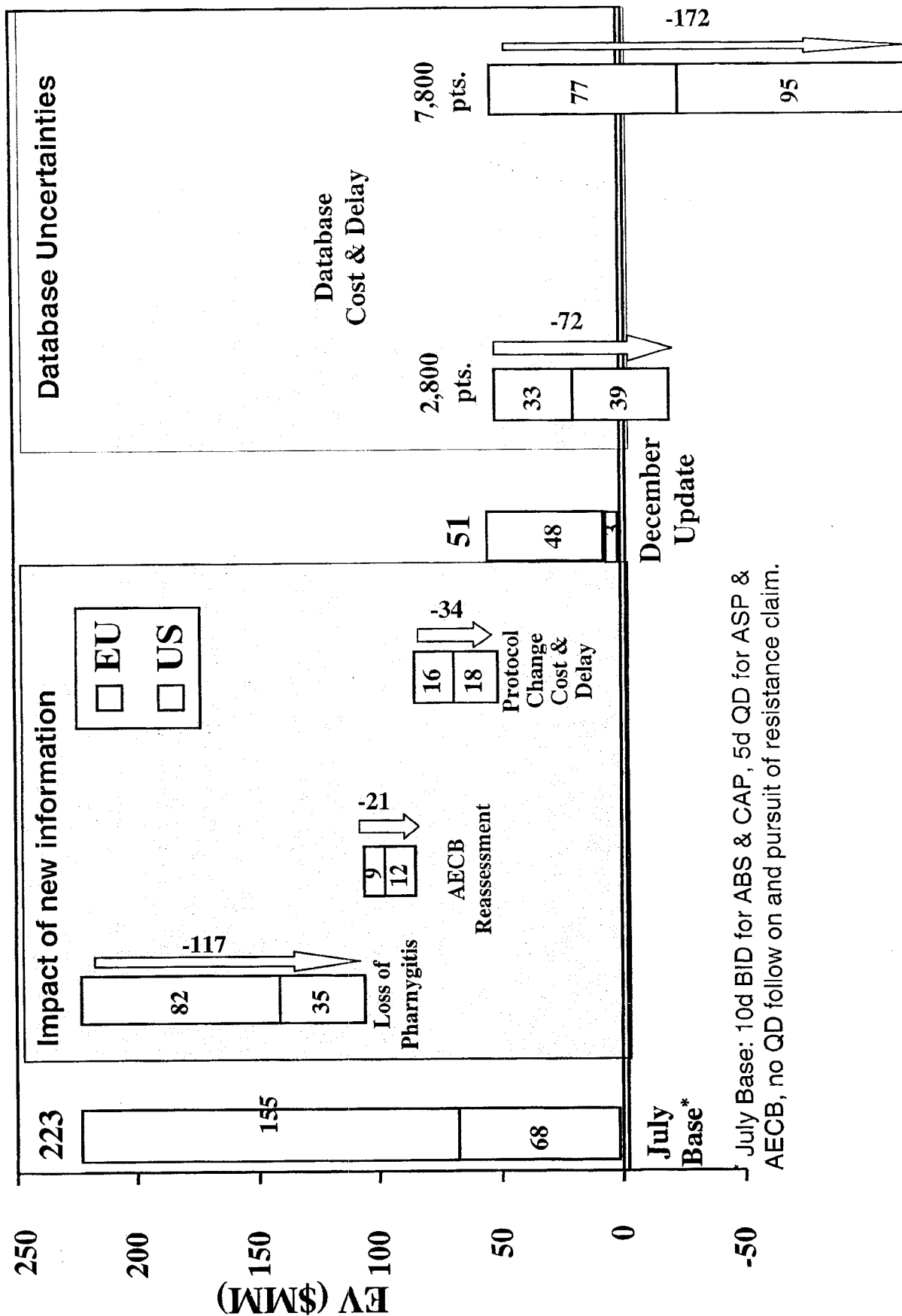
- QT issue still unresolved
  - Proposal to FDA (11/14/01) to recommence QT trial, if practicalities allow and data still acceptable – awaiting response
    - Open label without 450mg BID dose
    - Powering of trial diminished already from patient withdrawals
- LFTs
  - Protocol amendments to add Day 6 LFT monitoring to CAP/ABS trials and changes to informed consent will delay start
  - Amendments to informed consent for ongoing EU pivotals for ASP and ABECB will slow enrollment
  - Notification of dosing suspension of QT study to all regulatory agencies (that require it) has been done
  - Notify all IRB/Ethics Committees of impact

# Impact of Amendments on Phase III Pivotal Studies



\$MM	2002	2003	2004	Total
Current Tablet Budget	68.8	44.2		113.0
Estimate Revised Budget	63.0	53.0	9.0	125.0

# Value implications of recent ABT-773 information.



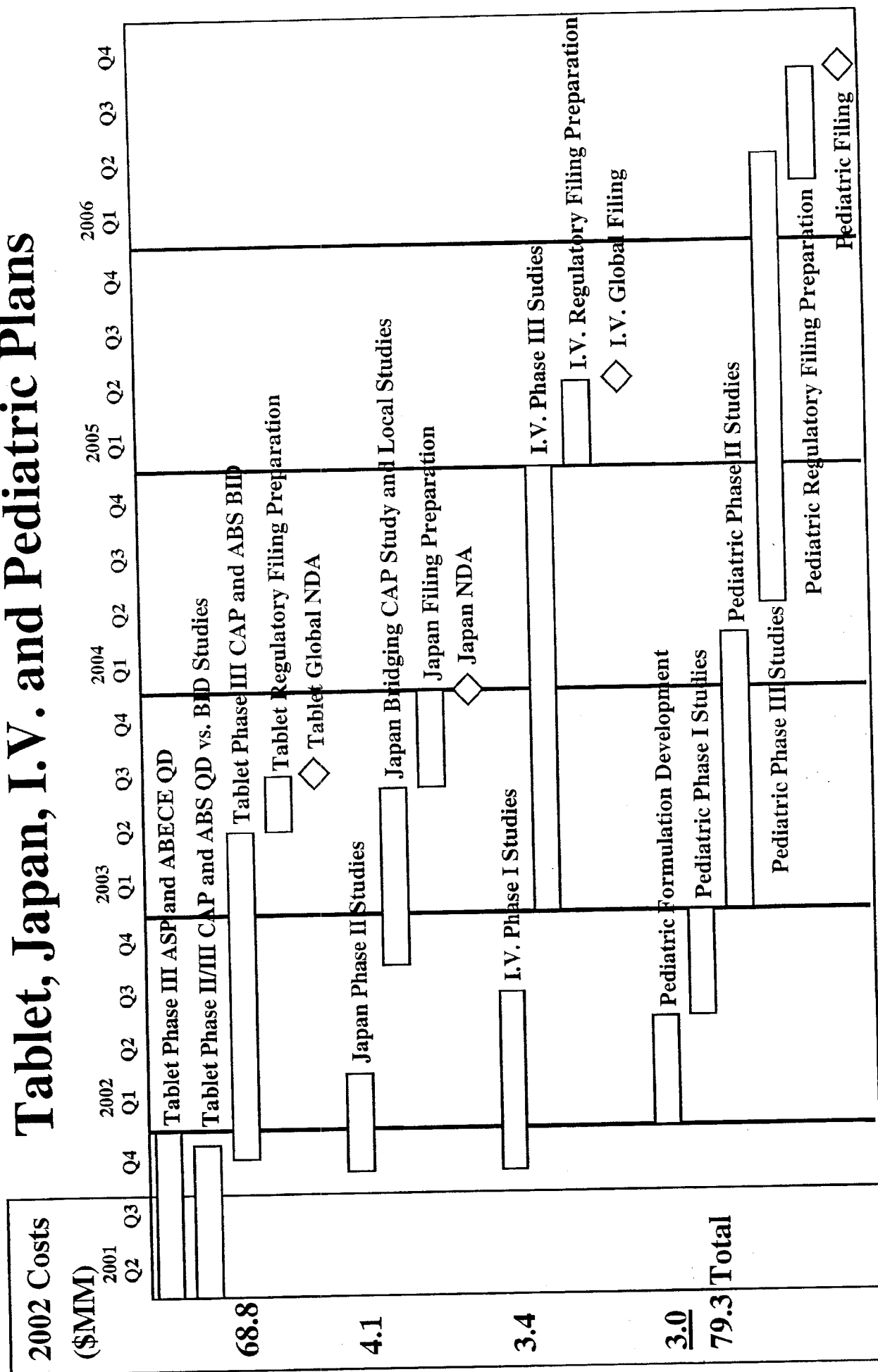
July Base: 10d BID for ABS & CAP, 5d QD for ASP & AECB, no QD follow on and pursuit of resistance claim.

Consider exiting ABT 773 Program due to drug profile changes, heightened regulatory risk and lowered NPV

Attribute	Planned	Current
QD dosing	ABECB/ASP QD CAP/ABS QD or BID w/QD follow on	CAP/ABS BID ASP QD ✖ ABECB QD?
Short-course therapy	ABECB/ ASP 5D CAP/ABS 10D	ABECB/ASP 5D CAP/ABS 10D
Efficacy with resistant organisms	Pursuing	Pursuing 15 isolates <b>Increased to 25 isolates ?</b>
Safety database	QT, liver	QT, liver Added 1000 patients
Cost	\$113MM	\$125.0MM
Timeline	Aug 2003	April 2004



# ABT-773 Development Program – Tablet, Japan, I.V. and Pediatric Plans

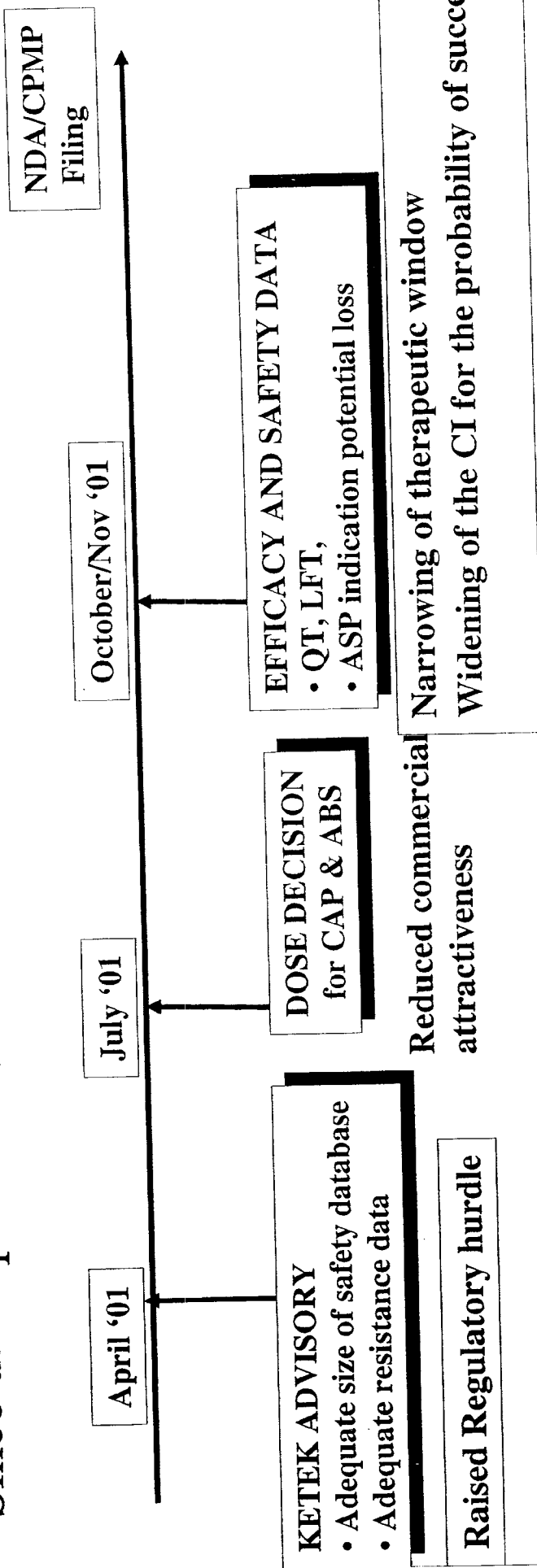


## Japan Impact of ABT 773 Program Developments

- Contractual agreement with Taisho Pharmaceuticals in Japan
- Phase I BAL and Phase II Open Label studies continuing as planned
- QD impact lower in Japan
- Impact of LFT abnormalities needs further evaluation
  - Will be re-assessed at EOP2a KIKO meeting
- Possible bridging strategy is dependent on US/EU filing

# ABT 773 Team Summary and Recommendations

Since the April PEC, the development plan has been impacted by:



**Summary:** Reducing NPV of the product

**Recommendation:** Do not complete development of ABT 773

# Timing of Actions with Assumptions

Exit Now	Initiate Ph III	Enroll 2 mo	Enroll 6 mo	Enroll 9 mo
Dec 2001	Jan 2002	Mar 2002	Jul 2002	Oct 2002
Close ongoing studies, cancel Phase III pivotals for CAP & ABS. Close IV and Peds development	Submit amendments to IRB/EC and initiate studies as soon as possible.	US enrollment ~150 ABS pts, 80 CAP pts.	US & EU enrollment slowed, end of season, Before So Hemisphere sites started	US & EU enrollment started again, So Hem sites enroll 100 CAP pts.
Avoids majority of external costs in 2002.	Maintain investigator relationships and support. Allow time to plan communication.	Data on ABECB US pivotal study will be available.	Japan KIKO mtg held, ABECB and ASP EU results, Ketolide back up could be ready to start development	Evaluate enrollment achieved and re-assess filing timeline.

# 2002 Exit Costs

<i>Activity</i>	Exit Now	Initiate Ph III	Enroll 2 mo	Enroll 6 mo	Enroll 9 mo
	Dec 2001	Jan 2002	Mar 2002	Jul 2002	Oct 2002
<i>Costs (\$MM)</i>					
<i>Internal</i>	12.2	20.3	28.6	36.2	40.0
<i>External</i>	4.3	11.7	15.0	19.8	21.3
<i>Total</i>	16.5	32.0	40.1	56.0	61.3

2002 Cost assumptions:

- No spending on Peds and IV programs
- Japan clinical costs to KIKO meeting
- 3 mo functional resources and 6 mo clinical resources for shut down activities

# PART 2

# Backups

# ABT-773 Adverse Events

## Phase 2b and Phase 3

Nausea	10% (197/2029)
Diarrhea	9% (192/2029)
Taste	9% (191/2029)
Headache	7% (149/2029)
Vomiting	5% (93/2029)



# ABT-773 Phase III Clinical Plan (Pivotal Trials)

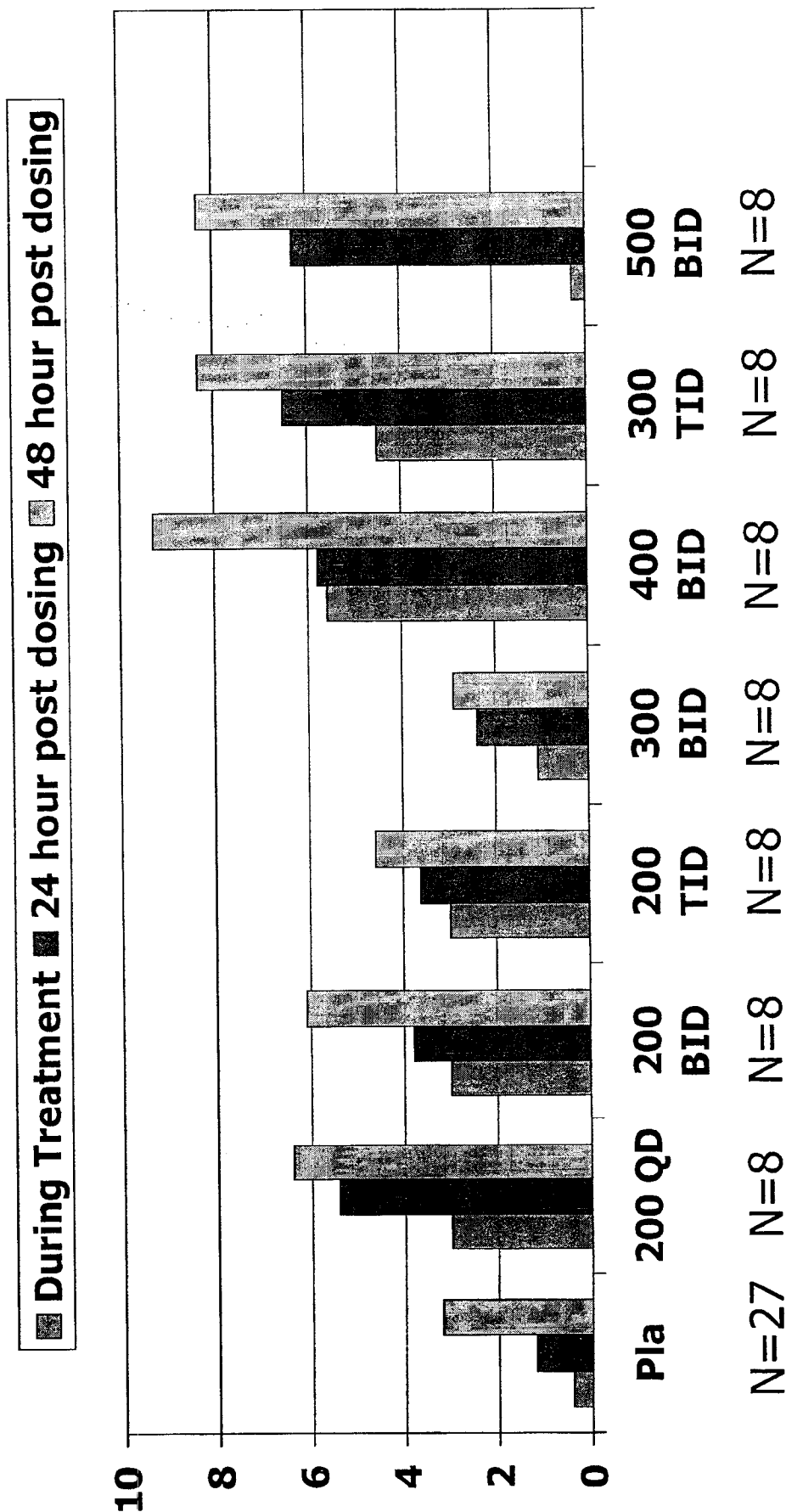
Study	Indication	Comparator	Team recommendations
US, EU (IND) M00-225	Sinusitis	NA	Enrollment has been stopped at 609 patients, close study without open label portion
US, Canada (IND)	Sinusitis	Augmentin	Submit protocol amendment, modify Informed consent, expect approval to start by mid January.
EU (Non-IND)	Sinusitis	Quinolone	Submit protocol amendment, modify Informed consent, expect approval to start by mid February in some countries, remainder in March.
US (IND) M00-219	CAP	NA	Enrollment has been stopped at 586 patients, close study.
US (IND)	CAP	Levofloxacin	Submit protocol amendment, modify Informed consent, expect approval to start by mid January.
EU (Non-IND)	CAP	Amoxicillin	Submit protocol amendment, modify Informed consent, expect approval to start by mid February in some countries, remainder in March.
US	Pharyngitis	Penicillin	Failed
EU	Pharyngitis	Penicillin	Continue enrollment (currently 209) to meet targets by end April 2002. Modify informed consent.
US	ABECB	Azithromycin	Enrollment target will be met by 12/5/01
EU	ABECB	Levofloxacin	Continue enrollment (currently 327) until target of 500 patients is met at end March 2002. Modify informed consent.

# Overall Incidence of LFT's Not Changed (All Subjects with LFT)

	$\geq 3 \times ULN$ Study			
	Normal Baseline $< 1 \times ULN$	Abnormal Baseline $1-3 \times ULN$	Significantly Abnormal Baseline $\geq 3 \times ULN$	Total
Original overall N=2884	13	17	9	39 (1.4%) [1.0, 1.8]
New overall N=2939	17	17	9	43 (1.5%) [1.1, 2.0]
Current phase 3 N=1047	4	7	6	17 (1.6%) [0.9, 2.6]

# Multiple Rising Dose Study (M97-796)

## Mean Change from Baseline in SGPT



# Timing of dosing does not make a difference

Shift Tables of SGPT in 300 mg Total Daily Dose in Phase 2 and 3

Studies	$>1*ULN$	$\geq 2*ULN$	$\geq 3*ULN$
M99-048 (5 days) AECB	10.9% (11/101)	1.7% (2/117)	2.5% (3/120)
M99-054 (7 days) CAP	26.1% (18/69)	5.1% (4/78)	2.5% (2/80)
M00-219 (10 days) CAP	11.5% (17/148)	3.5% (6/172)	1.7% (3/176)
M99-053 (10 days) ABS	10.5% (9/86)	1.1% (1/95)	0.0% (0/95)
M00-225 (10 days) ABS	10.8% (21/195)	1.9% (4/213)	0.5% (1/216)

## ABT 773 QT issues

- Re-read key Phase I and Phase II ECG data (6749 ECGs)-completed
- Phase III studies ECGs: Ongoing studies (9085 expected)-45% completed  
Planned studies (8000 expected)
- Dedicated Phase I QT evaluation study as agreed by FDA started Sept 01 (>9000 ECGs)
  - Four-period, double-blind, placebo-control crossover designTime-matched ECGs/PK samples at day-1, day1 and steady state on day 5

**TOTAL OF 34000 ECG's: Most with correlating plasma levels of ABT773**

# Regulatory experience defined new regulatory standards which determines program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
  - Ketek's 3200 patient safety database insufficient, ?liver/QT.
- A resistance claim will significantly support benefit risk:

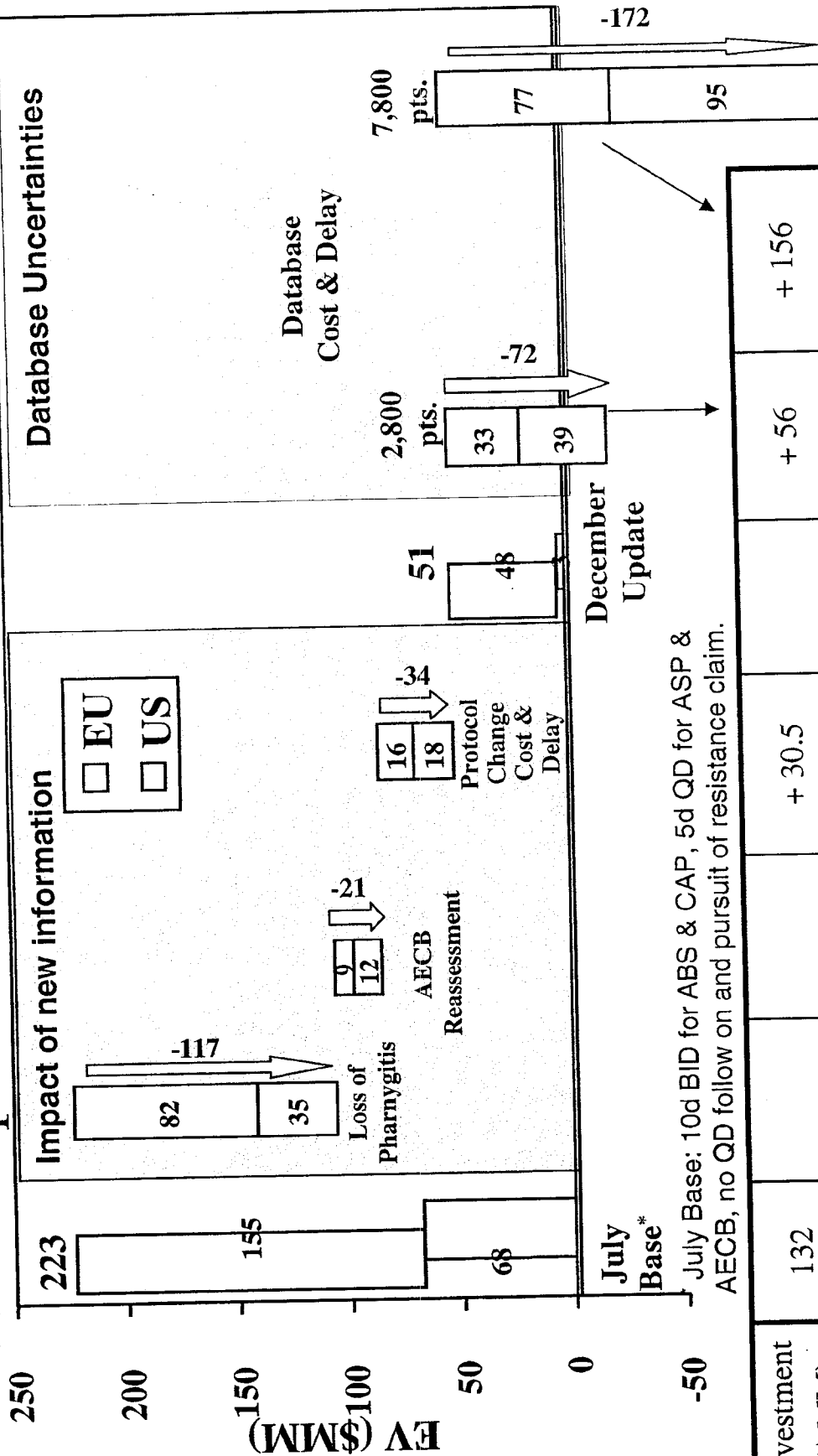
Isolates Needed	% CAP patients with PRSP/MRSP		
	1.4%	1.6%	3.2%
17	1236	1063	531
25	1818	1563	781
30	2182	1875	938

- Importance of CAP emphasized

Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
6. Expand the Phase III CAP program to allow for 3 arms per study – QD vs. BID vs. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop arm on result availability

# Value implications of recent ABT-773 information.

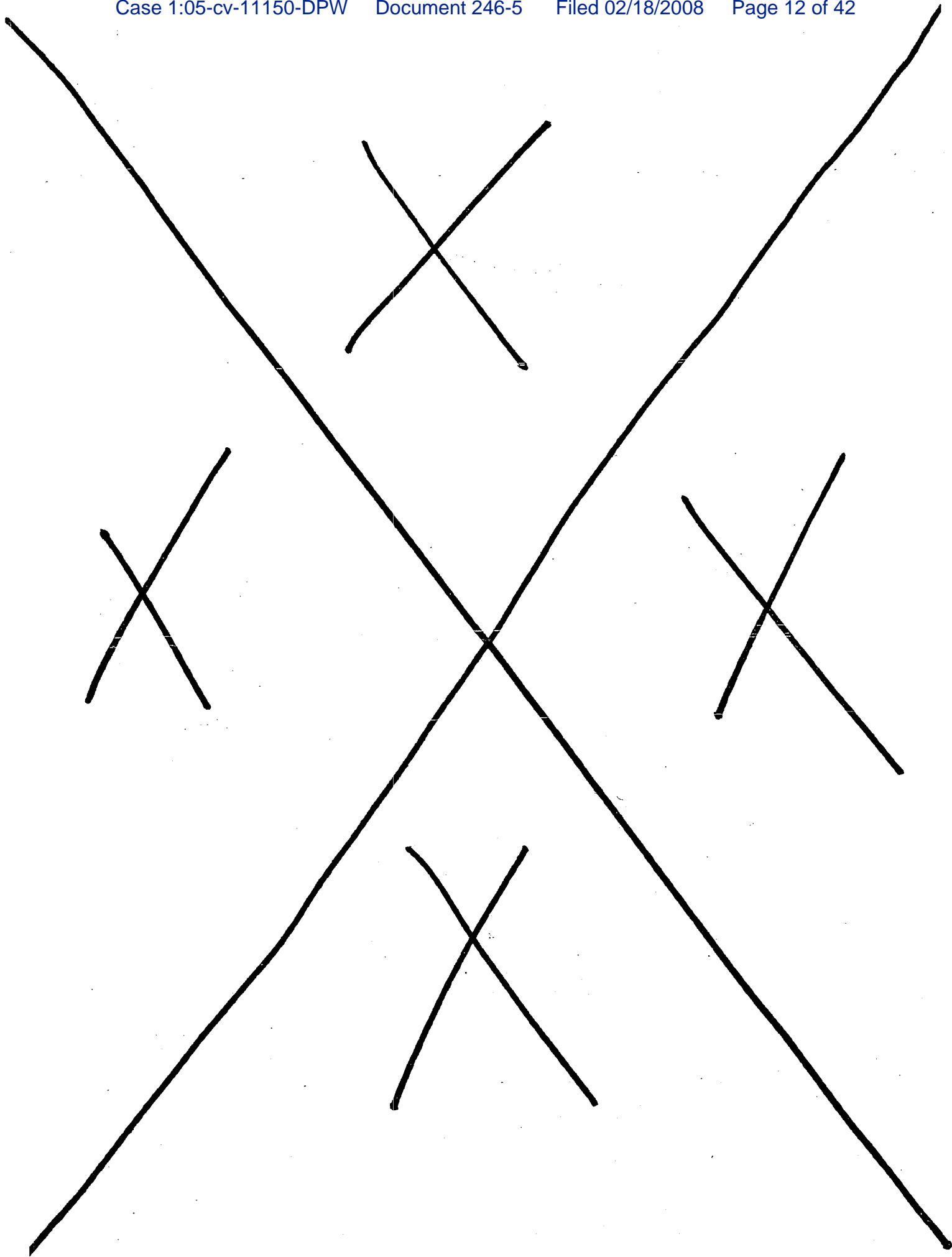


December Update

July Base: 10d BID for ABS & CAP, 5d QD for ASP & AECB, no QD follow on and pursuit of resistance claim.

Investment (\$ MM)	132	+ 30.5				+ 156
Launch Date	4Q04	4Q05				4Q07
Expected Peak Sales (\$ MM)						
Total	312	248	235	235	235	235
US	168	145	137	137	137	137
EU	145	103	99	99	99	99





**FI**



**FK**

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## GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

**Phase II Study of the Matrix Metalloprotease Inhibitor, Prinomastat in Patients with Progressive Breast Cancer.** H. S. Rugo, D. Budman, C. Vogel, S. Baidas, G. Fleming, M. Collier, M. Dixon, Y. Pithavala, N. J. Clendeninn, D. Tripathy, D. Hayes; University of California San Francisco, San Francisco, CA; North Shore University Hospital, Manhasset, NY; Columbia Cancer Research Network, Plantation, FL; Lombardi Cancer Center, Georgetown University, Washington, DC; University of Chicago, Chicago, IL; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA

Matrix metalloproteases (MMPs) are enzymes that degrade the extracellular matrix. Prinomastat (AG3340) is a potent MMP inhibitor designed using X-ray crystallography that reduced tumor angiogenesis, invasion, and metastasis in preclinical models. Patients (pts) having metastatic breast cancer that progressed on most recent therapy were randomized to 5 or 25 mg prinomastat administered orally twice daily. The rate of stable disease (SD), time-to-progression (TTP), potential biomarkers of MMP inhibition and the safety of single agent prinomastat were studied. 15 pts were to enroll into each treatment arm with expansion to 30 pts in an arm if at least one pt had SD at 8 weeks. A total of 44 female pts were enrolled. 29 pts received 5 mg and 15 pts received 25 mg prinomastat. Median age was 58 years (range 37-84), 93% of pts had failed chemotherapy in the metastatic setting, 55% had visceral metastases, and 70% had measurable disease. Musculoskeletal effects (hypothesized to be related to MMP inhibition) required treatment rest or discontinuation in 21% of pts at 5 mg between weeks 8-24 and 27% of pts at 25 mg between weeks 4-8. No objective disease responses were observed. Median TTP was 8 weeks in both arms, 9/29 pts in the 5 mg dose arm had SD at week 8, with 5 pts stable for at least 16 weeks. Preliminary analyses indicate that some biomarkers had potential prognostic value or paralleled disease progression. Low pretreatment plasma VEGF (<40pg/mL) and urine pyridinoline levels (<90pmol/ $\mu$ mol creatinine) correlated with SD at 8 weeks [67% vs 25% ( $p<0.05$ ), and 100% vs 42% ( $p<0.005$ ) for SD vs PD at week 8, respectively]. Further analyses of disease stabilization and correlative studies will be presented.

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## GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

**Survival Benefit of Trastuzumab (Herceptin) and Chemotherapy in Older (Age>60) Patients.** G. A. Fyfe, R. Mass, M. Murphy, D. Slamon; Genentech, Inc, South San Francisco, CA; University of California-Los Angeles, Los Angeles, CA

The pivotal trial of Herceptin (H) plus chemotherapy (C) (doxorubicin/epirubicin and cyclophosphamide (AC) or paclitaxel (T)) versus C alone in first-line therapy of metastatic breast cancer (MBC) demonstrated improved responses rate (RR) (50% versus 38%,  $p=0.003$ ) and improved survival (S) (odds ratio, 0.80,  $p=0.053$ ). This survival benefit was observed despite a design that resulted in 65% of control patients to receive H at disease progression. Eligibility for this trial was not restricted by age. We are reporting a retrospective exploratory analysis to determine the influence of age on clinical benefit from H in this trial. A total of 469 patients were enrolled; 360 (77%) age  $\leq 60$  and 109 (23%) age 60. Baseline characteristics were similar between the 2 groups with the following exceptions: age 60; worse baseline KPS (41% vs. 30%  $\leq 80$ ), higher initial nodal burden ( $\geq 4$ , 52% versus 34%) longer disease-free interval from adjuvant therapy (26 versus 20 mo.), more frequent prior exposure to hormonal therapy (71% vs. 54%), and less frequent adjuvant exposure to anthracyclines (31% vs. 40%). In the age  $\leq 60$  group, the addition of H to C improved RR from 33% to 52% and S from 23 to 26 mo. In the 60 group the addition of H to C improved RR from 28% to 44% and S from 14 to 19 mo. Cardiac dysfunction (CD) in the H + T arms occurred in 11% of the  $\leq 60$  group and 21% of the 60 group. All CD events in the 60 group improved to grade 1 and H was continued. Conclusions: The group of HER2+, age 60 appeared to have a worse overall outcome compared to the  $\leq 60$  group, possibly related to adverse baseline characteristics. However, the survival benefit in the age 60 group from the addition of H to C was significant (relative risk 0.64 95% CI: 0.41-0.99). These data suggest that older (age 60) patients with MBC should be considered for first-line H + C therapy.

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## GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

**Phase II Trial of a Doxorubicin, Docetaxel, and Cyclophosphamide Triplet (ATC) for Locally Advanced and Metastatic Breast Cancer: Preliminary Results from NSABP BP-58.** R. E. Smith, S. Anderson, B. Lembersky, N. Dimitrov, A. Desai, C. Kardinall, E. Marmounas; NSABP Operations and Biostatistical Center, Pittsburgh, PA

Based on the recommended Phase II doses for AT [doxorubicin (A: 60 mg/m<sup>2</sup>) plus docetaxel (T: 60 mg/m<sup>2</sup>) and the NSABP's experience with A plus C (Cyclophosphamide 600 mg/m<sup>2</sup>) (AC), we conducted a Phase II trial at 18 institutions using ATC q 21 days, in preparation for a major adjuvant breast cancer (BC) study (NSABP B-30) in which ATC would be used. Eligibility requirements included measurable stage IIIB/IV BC, performance status 0-2, normal LVEF, no prior chemo (except non-taxane adjuvant chemo, if completed >12 months before entry) and cumulative A [symbol:Symbol (PCL6)/1631240 mg/m<sup>2</sup>. Eighty-nine patients were entered: age range, 30-78 yrs (38.2% <50 yr; 61.8% [symbol:Symbol (PCL6)/179150 yrs); 33.7% with stage IIIB, 66.3% with stage IV BC; 20.3% stage IV pts, received prior adjuvant chemo. Dexamethasone premedication (8 mg po bid X 3 doses) and prophylactic ciprofloxacin (500 mg po bid days 5-15) were used. Growth factors (GF) were reserved for secondary prophylaxis after prolonged or febrile neutropenia (FN). When cumulative A = 480 mg/m<sup>2</sup>, pts could continue with TC alone. Results: 89 pts and 536 courses were evaluable for toxicity. Median time on study was 17.5 months (range = 9-28). FN occurred in 33 pts (37%); 10 had FN in the absence of GF support; 23 had FN despite GF support. There were no septic deaths. 1 pt died from pulmonary embolism. Other grade 3-4 adverse events included: nausea 9%, vomiting 7%, stomatitis 6%, diarrhea 4%, arthralgia/myalgia 3%, neurocortical 1%. Clinical CHF was seen in 4 pts (4%). To date, 58 pts are evaluable for best response: there has been CR in 5 pts (5.6%); PR in 39 pts (43.8%); SD in 9 (10%). Conclusions: ATC with primary ciprofloxacin and secondary GF prophylaxis is well tolerated and active. Its value in the adjuvant setting is currently under investigation. Presentation will include updates. (Supported by PHS grant U10CA12027 and Aventis Pharmaceuticals)

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## GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

**A Randomized Phase II Study of Alternating (AA) vs Sequential (SS) vs the Combination (CC) of Doxorubicin (A) and Docetaxel (T) as 1st Line CT in MBC.** S. Cresta, G. Grasselli, A. Martoni, G. Lelli, M. Mansutti, G. Capri, F. Buzzi, G. Robustelli, L. Frevola, S. Mekhaldi, N. Azli, L. Gianni; Istituto dei Tumori, Milan, Italy; Ospedale S. Orsola Malpighi, Bologna, Italy; Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Ospedale Santa Maria della Misericordia, Udine, Italy; Ospedale Civile Santa Maria, Terni, Italy; Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy; Aventis Pharma S.A., Lainate, Italy

Schedule of administration may affect the therapeutic results of active drugs. To test the optimal way of administering A and T in breast cancer patients, we performed a randomized trial comparing alternating administration (AA) of three-weekly A (75 mg/m<sup>2</sup>) plus T (100 mg/m<sup>2</sup>) for 8 overall cycles, vs. sequential (SS) A (4 cycles) followed by T (4 cycles) at the same doses, vs. combined (CC) A and T at 60 mg/m<sup>2</sup> each (8 cycles). From 1/1/96 to 01/00, 121 MBC patients were treated (AA=42; SS=38; CC=41). Patient characteristics were well balanced between arms: median age was 53 yrs (24-69), WHO PS 0 (0-1). Fifty-three patients (44%) had prior chemotherapy (16 prior anthracyclines) as adjuvant. Tumor involved 2 sites in 52, 45 and 32% of patients (arms AA, SS and CC, respectively). Visceral involvement was present in 74, 84 and 66%, and liver involvement in 45, 42, 46%. Median cycles was 8, median relative dose intensity higher than 0.9 for each drug in each arm. Febrile neutropenia (7, 0, 22%), grade 3/4 infections (0, 0, 2%), and grade 3/4 stomatitis (5, 5, 12%) were higher in arm CC. At median 22 months of follow-up, four episodes of congestive heart failure occurred in arm CC (10%) at cumulative A dose of 480 mg/m<sup>2</sup>. The overall response rate was similar in all arms (57, 67 and 66%, respectively). Time to progression was 34, 33 and 36 weeks, respectively. Analysis of survival is too early. In conclusion, all schedules of A and T were feasible and active as first line treatment for MBC. The combination regimen was more toxic, and the higher cumulative dose of A in that arm explains the observed cardiac toxicity. Survival data and further Phase III investigations will clarify the respective merits of the different schedules.

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692 ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

**Interim Results of a Phase III Study of the Matrix Metalloproteinase Inhibitor Prinomastat in Patients Having Metastatic, Hormone Refractory Prostate Cancer (HRPC).** F. R. Ahmann, F. Saad, R. Mercier, R. A. Huddart, J. T. Roberts, M. Collier, L. Bettencourt, M. H. Zhang, N. J. Clendeninn, G. Wilding; Arizona Cancer Center, Tucson, AZ; CHUM-Notre Dame, Montreal, Canada; Marshfield Clinic, Marshfield, WI; The Royal Marsden, Sutton, UK; Newcastle General Hospital, Newcastle, UK; Agouron Pharmaceuticals Inc., A Pfizer Company, La Jolla, CA; University of Wisconsin, Madison, WI

Matrix metalloproteinases (MMPs) degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG3340) is a potent inhibitor of MMPs that demonstrated efficacy in preclinical in vivo tumor models. A phase III trial investigated prinomastat in combination with mitoxantrone (M) and prednisone (P) in chemotherapy naive patients (pts) having metastatic HRPC. M was administered intravenously at 12 mg/m<sup>2</sup> q3weeks and P orally, 5mg twice daily. Pts were randomized to 5 or 10mg prinomastat or placebo, orally twice daily. Between 4/98 and 7/00, 553 pts were enrolled; interim results are available for 406 pts. Baseline characteristics were balanced with median age 71 years, median PSA 94 ng/mL and 33% measurable disease. M+P dose-intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and, rarely, tendinous contracture. Grade-2 MS were observed in 13, 22 and 22% of pts in the placebo, 5 and 10mg arms, respectively; events persisting for at least 3 weeks were managed by treatment-rest and prinomastat dose reduction. No differences were observed among the treatment arms in PSA response rate (RR, 75% reduction for 3wks); progression-free survival by radiography (RPFS), PSA (50% increase for 3wks), or symptoms (SPFS); or overall (OS) and 1-year survival. Efficacy was not enhanced by the addition of prinomastat to M+P in pts having metastatic HRPC.

**Efficacy Parameters**

	Patients	PSA/RR	Median (months)				1-Year Survival
	Randomized	(%)	RPFS	PSA/PFS	SPFS	OS	(%)
M+P-Placebo	138	14	6.0	6.8	7.7	14.8	60
M+P-5mg	134	17	6.0	8.9	8.6	15.1	64
M+P-10mg	134	18	4.7	6.5	8.3	14.7	63

694 ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

**The Endothelin-A Receptor Antagonist Atrasentan (ABT-627) Delays Clinical Progression in Hormone Refractory Prostate Cancer: a Multinational, Randomized, Double-Blind, Placebo-Controlled Trial.** M. A. Carducci, J. B. Nelson, R. J. Padley, T. Janus, R. Hippensteel; Johns Hopkins University, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Abbott Laboratories, Abbott Park, IL

In hormone refractory prostate cancer (HRPCa), death is typically preceded by painful, osteoblastic skeletal metastases. Pre-clinical studies indicate that endothelin-1, via the endothelin-A receptor, inhibits apoptosis, stimulates proliferation of prostate cancer cells and osteoblasts, and is nociceptive. We evaluated atrasentan, a highly-potent (K<sub>i</sub>=34 pM), selective (1800-fold), orally bioavailable, endothelin-A receptor antagonist as a treatment for men with HRPCa. Castrate patients, with adequate anti-androgen withdrawal, were randomized to placebo (n=104), 2.5mg atrasentan (n=95) or 10mg atrasentan (n=89) once daily. 244 patients were evaluable for the primary endpoint of time to clinical progression, defined as a disease-related event requiring intervention, disease-related pain requiring opiate therapy, or new lesions on imaging studies. Secondary endpoints included time to PSA progression, biochemical measures of metastatic progression and quality of life. Atrasentan patients had a statistically significant delay in time to clinical progression (2.5mg, 10mg) and PSA progression (10mg) compared to placebo. Atrasentan attenuated markers of metastatic progression including acid phosphatase, LDH, and alkaline phosphatase (p<0.05). The most common treatment-related adverse events (10mg vs. placebo) included peripheral edema (35% vs 14%), rhinitis (28% vs 13%), and headache (20% vs 10%), which were mild to moderate in nature and resulted in few discontinuations. No differences in treatment-emergent grade 3/4 toxicities were observed. Atrasentan sustained a favorable health status for a greater duration as determined by performance status and measurement of quality of life. Atrasentan represents a new, well-tolerated, oral, cytostatic therapeutic paradigm for men with HRPCa.

	Placebo	2.5mg Atrasentan	10mg Atrasentan
Median Time to Clinical Progression	129 days	184 days*	196 days*
Median Time to PSA Progression	71 days	134 days	155 days*

\*Log-Rank test vs Placebo (p<0.05)

693 ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

**Preliminary Evidence That Oral Clodronate Delays Symptomatic Progression of Bone Metastases from Prostate Cancer: First Results of the MRC PRO5 Trial.** D. P. Dearnaley, M. R. Sydes, on behalf of the MRC PRO5 collaborators; The Institute of Cancer Research and Royal Marsden NHS Trust, Sutton, UK; MRC Clinical Trials Unit, London, UK

BACKGROUND: Bone is the most common site of metastases from prostate cancer (PCa). Bisphosphonates have been shown to slow development of metastases from breast cancer and myeloma and to modify bone pain in skeletal metastases from PCa. DESIGN: Phase III double-blind placebo-controlled randomised controlled trial of oral bisphosphonate in men commencing or responding to standard hormonal treatment. Primary endpoint: time to development of symptomatic bone progression or PCa death. TREATMENT: Either (A) 4 tablets/day (2,080mg) of oral sodium clodronate (Loron 520) or (C) 4 tablets/day of matching placebo. Patients (pts) were encouraged to stay on trial medication for 3 yrs or until the primary trial endpoint had been reached. RESULTS: Patients: 311 pts were randomised over 4yrs (6/94-7/98): 156A, 155C. Baseline characteristics were well balanced. Median follow-up to date is 3 years. Medication & Toxicity: Median time on trial medication was 18 months(m) for A (95%CI 15-21) and 16m (95%CI 12-20) for C. 259 patients have stopped trial medication, 29 (13A, 16C) after 3 years of treatment, 155 (65A, 90C) after symptomatic bone progression and 75 (48A, 27C) because of Adverse Events (AEs) or pt preference. AEs were reported more often for A (118AEs/75pts vs 69AEs/48pts, Relative Risk=1.79, p=0.0014) & required modification of trial medication dose more often (52 vs 20 pts, p=0.0001). Gastro-intestinal problems and raised LDH were the most common adverse events. Primary Endpoint: 202 patients have reached primary trial endpoint, 93 A and 108 C; Hazard Ratio (HR)=0.75 (95%CI 0.57-0.99) in favour of A (p=0.044). At 2yrs, 51% (95%CI 44-59) A and 41% (95%CI 33-49) C had not reached primary endpoint. Median time to primary endpoint is 26m (95%CI 21-31) for A and 20m (95%CI 16-23) for C. Survival: 82 A and 94 C patients have died; HR=0.80 (95%CI 0.59-1.07) in favour of A (p=0.13). At 2yrs survival is 66% for A and 59% for C. Median survival is 34m for A and 27m for C. COMMENTS: These preliminary results provide evidence that oral sodium clodronate delays progression to symptoms from bone metastases in PCa. Updated results will be presented at the meeting.

695 ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

**A Prospective Randomized Trial of Antiandrogen Withdrawal Alone or Antiandrogen Withdrawal in Combination with High-Dose Ketoconazole in Androgen Independent Prostate Cancer Patients: Results of CALGB 9583.** E. J. Small, S. Halabi, J. Picus, N. Dawson, Y. Chen, N. J. Vogelzang; University of California, San Francisco, San Francisco, CA; Duke University, Durham, NC; Washington University, St. Louis, MO; University of MD, Baltimore, MD; University of Chicago, Chicago, IL

High-dose ketoconazole (HDK) has been shown in several phase II trials to reduce PSA levels in approximately 50% of androgen-independent prostate cancer (AiPCa) patients, with variable durations of response reported. CALGB 9583 sought to compare the response proportion and duration of response to antiandrogen withdrawal (AAWD) alone versus AAWD combined with HDK. "PSA response" was defined per consensus criteria. 261 AiPCa patients were randomized to AAWD alone (N = 132), followed by "crossover" to HDK at progression or to AAWD plus simultaneous HDK (N = 128). Ketoconazole, 400 mg p.o. t.i.d., was dosed with hydrocortisone, 40 mg p.o. q.d. Results are summarized below. These data suggest that the "PSA response" to AAWD in a large multicenter prospective cohort is modest, at 13%. Response to AAWD + HDK was higher (27%), but still lower than previously reported. There was no difference in survival in ear versus later use of HDK, and overall toxicity was modest.

	AAWD alone (n = 132)	AAWD + HDK (n = 128)	P value
PSA response	13%	27%	0.012
Objective response	4%	13%	0.012
Survival (incl. crossover pts)	16 mos.	15 mos.	0.792
Grade 3/4 toxicity	4%	22%	0.002



FL


cc:  
Subject: MMP CSR


Sue,

I will send the CSR to John this afternoon. Here is the scoop. They are going to make 6000 25 mg capsules now. They won't be able to make the entire 10060 at once. They will make 200 mg capsules in December. They never were going to make 200 mg caps now. I told Tamara to get in touch with you if she needs anything else.

Kysa

----- Forwarded by Susan M Glad/LAKE/PPRD/ABBOTT on 10/19/2000 11:42 AM

 Robert Hansen  
07/19/2000 07:59 AM

To: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: MMP CSR 

Susan

Did Kysa calculate her numbers from the supply spread sheet on the L: drive?

Bob


----- Forwarded by Susan M Glad/LAKE/PPRD/ABBOTT on 10/19/2000 11:42 AM

 Jackie A Schroeder 07/21/2000 03:04 AM

To: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: CDA - Dr. Zonnenberg

I received the signed, faxed CDA from Dr. Zonnenberg this morning.

----- Forwarded by Susan M Glad/LAKE/PPRD/ABBOTT on 10/19/2000 11:42 AM

 Robin A Rothkopf  
08/07/2000 08:15 AM

To: Susan M Glad/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT,  
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cc:  
Subject: MMPI press release

**Pfizer halted phase III clinical trials of prinomastat, a matrix metalloprotease inhibitor, in advanced hormone refractory prostate cancer and advanced non-small cell lung cancer, on failure to meet primary efficacy objectives .**

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Date: Monday, August 7, 2000  
Source: Bridge Information Systems, Inc.  
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Bridge Information Systems, Inc. via NewsEdge Corporation : By BridgeNews

New York--Aug 4--Pfizer halted phase III clinical trials of prinomastat, a matrix metalloprotease inhibitor, in advanced hormone refractory prostate cancer and advanced non-small cell lung cancer, on failure to meet primary efficacy objectives. The company intends to continue exploration of prinomastat in other tumor types and in earlier stage disease. Pfizer said four phase II trials are currently underway and two additional phase II trials will begin shortly.

--Rajendra Palande, BridgeNews

The following is the text of today's announcement with emphasis added by BridgeNews BridgeStation links to company data have been inserted at the end Pfizer Discontinues Phase III Trials of Prinomastat in Advanced Cancers but

NEW YORK and LA JOLLA, Calif., August 4 -- PFIZER (NYSE: PFE) ANNOUNCED TODAY THAT PRELIMINARY RESULTS OF PHASE III CLINICAL TRIALS OF PRINOMASTAT, A MATRIX METALLOPROTEASE INHIBITOR (MMPI), IN ADVANCED HORMONE REFRACTORY PROSTATE CANCER AND ADVANCED (STAGE IV) NON-SMALL CELL LUNG CANCER DID NOT MEET PRIMARY EFFICACY OBJECTIVES. NEITHER DETRIMENTAL NOR CONVINCING BENEFICIAL EFFECT OF THE COMBINATION OF PRINOMASTAT WITH STANDARD CHEMOTHERAPY WAS OBSERVED. CONSEQUENTLY, PFIZER IS HALTING THESE TWO PHASE III TRIALS.

Based on input from the Data Safety Monitoring Board (DSMB), patients having earlier stage (Stage IIIB) disease recruited into a second on-going non-small cell lung cancer trial will continue to be studied. THE COMPANY INTENDS TO CONTINUE EXPLORATION OF PRINOMASTAT IN OTHER TUMOR TYPES AND MOST IMPORTANTLY, IN EARLIER STAGE DISEASE, WHERE ONCOLOGISTS BELIEVE INHIBITION OF ANGIOGENESIS MAY HAVE GREATER UTILITY. FOUR PHASE II TRIALS ARE CURRENTLY UNDERWAY AND TWO ADDITIONAL PHASE II TRIALS WILL BEGIN SHORTLY.

Pfizer conducted multi-center, randomized, double-blind, placebo controlled trials to evaluate the safety and efficacy of prinomastat in combination with standard chemotherapy in patients with advanced hormone refractory prostate cancer and non-small cell lung cancer. Safety was not a factor in the decision to halt these trials. The details of the trial results will be presented on a later date in a scientific forum.

"Although we are disappointed in the outcome of these trials, we intend to continue exploration of prinomastat, and remain very interested in the field of MMPI research, and are committed to the many novel approaches to the treatment of cancer under development in our laboratories. The Phase II clinical trials of prinomastat underway and planned in different tumor settings and earlier stage disease should provide critical information relative to earlier intervention of angiogenesis," said Barry Quart, Pharm.D., Head of Pfizer Global Research and Development, La Jolla Laboratories

Pfizer Global Research and Development, La Jolla Laboratories is the Research and Development component of Agouron, a wholly owned entity of Pfizer Inc (NYSE: PFE), and are committed to the discovery, development, and marketing of innovative therapeutic products engineered to inactive proteins that play key roles in cancer, AIDS, and other serious diseases.

Pfizer Inc, the world's largest pharmaceutical company, discovers, develops, manufactures and markets leading prescription medicines, for humans and animals, and many of the world's best known over-the-counter brands. This year, Pfizer expects global sales of more than \$31 billion and has a research and development budget of \$4.7 billion.

SOURCE Pfizer Inc

/CONTACT: Sonia Anchundo, La Jolla, 858-622-7340, Andy McCormick, 212-573-1226, both of Pfizer Inc/

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**John Hancock Attendees**

Stephen Blewitt,  
Managing Director

Brewster Lee, Attorney  
Choate, Hall & Stewart

Kevin Tormey, Attorney  
Choate, Hall & Stewart

Amy Weed, Counsel  
John Hancock

**Abbott Attendees**

Arthur Higgins, Sr. Vice President,  
Pharmaceutical Products

Tom Freyman, Sr. Vice President,  
Finance and Chief Financial Officer

Bob Funck, Divisional Vice President  
and Controller, Global Pharmaceutical  
Research and Development & Portfolio Analysis

John Leonard, Vice President,  
Global Pharmaceutical Drug Development

Daphne Pals, Senior Counsel

Philip Deemer, Director,  
Corporate Licensing

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Abbott Laboratories  
invites you to a celebration of the  
closing of the  
John Hancock - Abbott Financing

Please join us for dinner

Monday, April 30, 2001

Carlos' Restaurant  
429 Temple Avenue  
Highland Park, IL 60035  
847-432-0770

Cocktails at 6:00 P.M.  
Dinner at 6:30 P.M.

Jacket and tie required

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RESEARCH FUNDING AGREEMENT

by and between

ABBOTT LABORATORIES

and

JOHN HANCOCK LIFE INSURANCE COMPANY,

JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY,

and

INVESTORS PARTNER LIFE INSURANCE COMPANY

dated as of

March 13, 2001

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RESEARCH FUNDING AGREEMENT

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and

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dated as of

March 13, 2001

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## RESEARCH FUNDING AGREEMENT

This Research Funding Agreement is made as of March 13, 2001, by and between Abbott Laboratories, an Illinois corporation ("Abbott"), with its principal offices at 100 Abbott Park Road, Abbott Park, Illinois 60064-6049, and John Hancock Life Insurance Company, a Massachusetts corporation, John Hancock Variable Life Insurance Company, a Massachusetts corporation, and Investors Partner Life Insurance Company, a Delaware corporation (collectively, "John Hancock"), each with its principal offices at 200 Clarendon Street, Boston, Massachusetts 02117.

### WITNESSETH

WHEREAS, Abbott is a global healthcare company actively engaged in the research and development of human pharmaceutical products;

WHEREAS, Abbott is interested in obtaining additional funding to support such research and development activities with respect to certain pharmaceutical products which are under development; and

WHEREAS, John Hancock is interested in providing such additional funding in exchange for the right to receive future milestone and royalty payments from Abbott.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants and undertakings contained herein, the parties hereto agree as follows:

### ARTICLE I DEFINITIONS

In addition to the other terms defined elsewhere herein, the following terms shall have the following meanings when used in this Agreement (and any term defined in the singular shall have the same meaning when used in the plural and vice versa, unless stated otherwise):

1.1 "Affiliate" shall mean, with respect to each party, any corporation or other form of business organization, which directly or indirectly owns, controls, is controlled by, or is under common control with, such party. An entity shall be regarded as being in control of another entity if the former entity has the direct or indirect power to order or cause the direction of the policies of the other entity whether (i) through the ownership of more than fifty percent (50%) in the United States, or thirty percent (30%) or more outside the United States, of the outstanding voting securities (or other ownership interest for a business organization other than a corporation) of that entity; or (ii) by contract, statute, regulation or otherwise.

1.2 "Aggregate Carryover Amount" shall have the meaning given in Section 3.3.

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1.3 "Aggregate Spending Target" shall mean Six Hundred Fourteen Million Dollars (\$614,000,000).

1.4 "Annual Carryover Amount" shall have the meaning given in Section 3.3.

1.5 "Annual Minimum Spending Target" for each Program Year, shall mean the sum of (i) the Program Payment of John Hancock for such Program Year as specified in Section 3.1, (ii) Fifty Million Dollars (\$50,000,000), and (iii) any Annual Carryover Amount for the prior Program Year pursuant to Section 3.3. With respect to the fifth Program Year, the "Annual Minimum Spending Target" shall mean the Annual Carryover Amount for the prior Program Year pursuant to Section 3.3.

1.6 "Annual Research Plan" shall mean, for the Program Years in the Program Term, a reasonably and consistently detailed statement of the objectives, activities, timetable and budget for the Research Program for every Program Year remaining in the Program Term, it being understood that less detail shall be required for Program Years that are not the current Program Year. The first Annual Research Plan is attached as Exhibit 1.6. "Annual Research Plan" shall mean, for those years occurring after the expiration of the Program Term, a reasonably and consistently detailed statement of the objectives, activities, timetable and budget for the Research Program for such year only.

1.7 "Bundled Product" shall have the meaning given in paragraph (b) of the definition of Net Sales.

1.8 "Ceased Program" shall mean at least one year has elapsed since Abbott ceased its directed efforts with respect to the applicable Preclinical Program (FTI Program, ED Program or MMPI Program), meaning that Abbott has eliminated the funding for the established research program identified by a core group of researchers dedicated to the applicable Preclinical Program. The continued existence of a researcher separate and apart from such core group shall not affect the determination that a Preclinical Program has ceased.

1.9 "Combination Product" shall mean any product containing one or more Program Compounds combined as a single pharmaceutical product with one or more other therapeutically active ingredients.

1.10 "Commercially Reasonable Efforts" shall mean efforts which are consistent with those normally used by other pharmaceutical companies with respect to other pharmaceutical compounds or products which are of comparable potential commercial value and market potential at a similar stage of development or product life, taking into account, without limitation, issues of safety and efficacy, compound or product profile, proprietary status, the regulatory environment and the status of the compound or product and other relevant scientific factors.

1.11 "Compound Reports" shall have the meaning given in Section 12.2(i).

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1.12 "Confidential Information" shall have the meaning given in Section 10.2.

1.13 "Delivery System Product" shall have the meaning given in paragraph (d) of the definition of Net Sales.

1.14 "Dollars" or "\$" shall mean United States dollars.

1.15 "ED Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) which modulate dopamine receptors for the purpose of treating erectile dysfunction.

1.16 "Eisai Agreement" shall mean the License Agreement dated June 29, 2000 between Eisai Co., Ltd. and Abbott related to the Program Compound known as ABT-751.

1.17 "Eisai Territory" shall mean the countries listed on Exhibit 1.17 hereto.

1.18 "Execution Date" shall mean the date set forth in the introductory paragraph to this Agreement.

1.19 [Intentionally Omitted.]

1.20 "FDA" shall mean the U.S. Food and Drug Administration or any successor entity thereto.

1.21 "First Commercial Sale" shall mean the first sale of a Product in a given country by Abbott, its Affiliates or Licensees to an unaffiliated third person after Regulatory Approval has been granted in such country.

1.22 "FTI Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) which act as farnesyl transferase inhibitors for the purpose of treating cancer.

1.23 "In-License Agreements" shall mean the Eisai Agreement, the Wakunaga Agreement and the Taisho Agreement.

1.24 "International Territory" shall mean all areas of the world outside the U.S. Territory.

1.25 "Investigational New Drug Application" shall mean an investigational new drug application filed with the FDA in order to commence human clinical testing of a drug in the United States.

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1.26 "Licensee" shall mean any party licensed or otherwise authorized in writing by Abbott, its Affiliates or its licensees to market, distribute or sell Products and from whom Abbott receives a royalty or other payment based upon sales of Products by such party, its affiliates or its licensees (it being understood that a party that is a merely a distributor, wholesaler or similar reseller of Products is not a Licensee hereunder). In no case shall Eisai Co., Ltd. or Taisho Pharmaceutical Co., Ltd. be considered Licensees under the terms of the Eisai Agreement or Taisho Co-Development Agreement with respect to the Eisai Territory or Japan, respectively.

1.27 "Losses" shall mean any claims, demands, liabilities, costs, damages, judgments, settlements and other reasonable expenses (including attorneys' fees).

1.28 "Milestone Payment" shall have the meaning given in Section 6.3.

1.29 "MMPI Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) that inhibit matrix metalloproteinase and treat cancer.

1.30 "NDA" shall mean a New Drug Application (as defined by the FDA) filed with the FDA for the purpose of obtaining Regulatory Approval of a Product in the U.S. Territory.

1.31 "Net Sales" shall mean:

- (a) the total gross sales of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products), in each case as set forth on the invoices for such sales by Abbott, its Affiliates and Licensees to unaffiliated third parties in any given period, plus, if applicable, the fair market value of all properties and services received in consideration of a sale of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products) by Abbott, its Affiliates and Licensees to unaffiliated third parties during such period, less the following deductions directly paid or actually incurred by Abbott, its Affiliates or Licensees during such period with respect to the sale of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products) to the extent included in the gross invoiced sales price therefor:
  - (i) discounts, credits, rebates, allowances, adjustments, rejections, recalls and returns;
  - (ii) price reductions or rebates, retroactive or otherwise, imposed by government authorities;
  - (iii) sales, excise, turnover, inventory, value-added and similar taxes assessed on the royalty-bearing sale of Products;



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- (iv) transportation, importation, insurance and other handling expenses directly chargeable to the royalty-bearing sale of Products;
  - (v) charge backs granted to unaffiliated drug wholesalers; and
  - (vi) the portion of management fees paid to unaffiliated group purchasing organizations that relate specifically to the royalty-bearing sale of Products.
- (b) With respect to a Product which is sold together with any other products and/or services in a country at a unit price, whether packaged together or separately (a "Bundled Product"), the Net Sales of such Bundled Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Bundled Product shall be determined on a country-by-country basis as follows:
- (i) multiply the Net Sales of such Bundled Product in such country by the fraction  $A/(A+B)$  where A is the average selling price of such Product in such country when sold separately and B is the total of the average selling prices in such country of each such other product(s) and/or service(s) in such Bundled Product when sold separately; or
  - (ii) if (x) either the average selling price of such Product or the total of the average selling prices of each such other products and/or services in such Bundled Product in such country is not available as of such date or (y) such Product is not sold separately in such country, multiply the Net Sales of such Bundled Product in such country by a percentage determined by the mutual agreement of the Parties which represents the proportionate economic value in such country of such Product relative to the economic value in such country contributed by the other products and/or services in such Bundled Product.
- (c) With respect to a Combination Product, the Net Sales of such Combination Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Combination Product shall be determined on a country-by-country basis as follows:
- (i) multiply the Net Sales of such Combination Product in such country by the fraction  $A/(A+B)$ , where A is the total of the average selling prices of the Program Compounds in such

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Combination Product when sold separately in such country and B is the total of the average selling prices of each other therapeutically active ingredient when sold alone as a pharmaceutical product in such country; or

- (ii) if (x) either the average selling price of all Program Compounds in such Combination Product or the total of the average selling prices of each other therapeutically active ingredient in such Combination Product in such country is not available or (y) such Program Compounds are not sold separately in such country, multiply the Net Sales of such Combination Product by a percentage determined by mutual agreement of the Parties, which represents the proportionate economic value in such country of all Program Compounds in such Combination Product relative to the economic value in such country contributed by all other therapeutically active ingredients in such Combination Product.
- (d) For purposes of this paragraph (d), a "Premium Delivery System" means any delivery system comprising device(s), equipment, instrumentation or other non-ingestible components (but not solely containers or packaging) designed to assist in the administration of a Product, such as the Abbott ADD-Vantage® System. With respect to a Product which is sold together with a Premium Delivery System (a "Delivery System Product") in a country at a unit price, the Net Sales of such Delivery System Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Product shall be determined on a country-by-country basis as follows:
  - (i) if the Product is sold separately without the Premium Delivery System in a country, reduce the Net Sales of such Delivery System Product in such country by the amount that the average selling price of the Delivery System Product in such country exceeds the average selling price of such Product as sold separately in such country; or
  - (ii) if the Product is not sold separately without the Premium Delivery System in such country, reduce Net Sales of such Delivery System Product by an amount, determined by mutual agreement of the Parties, which represents the proportionate economic value in such country added by the Premium Delivery System.
- (e) Net Sales shall not include any sales of Products containing one Program Compound (and no other Program Compound) known as (i) ABT-751 by Eisai Co. Ltd., its affiliates or licensees in the Eisai Territory or (ii) ABT-



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773 by Taisho Pharmaceutical Co., Ltd., its affiliates or licensees in Japan. Notwithstanding the foregoing sentence, Net Sales shall include in all instances sales by such parties of such products that are outside such territories, respectively.

1.32 "Parties" shall mean Abbott and John Hancock.

1.33 "Patents" shall have the meaning set forth in Section 12.2(e).

1.34 "Phase I Clinical Trial" shall mean a clinical trial of a Program Compound which utilizes a limited number of human beings preliminarily to address safety and to determine what doses can be safely tolerated.

1.35 "Phase II Clinical Trial" shall mean a controlled clinical trial, the primary objective of which is to ascertain additional data regarding the safety and tolerance of one of the Program Compounds and preliminary data regarding such Program Compound's efficacy.

1.36 "Phase III Clinical Trial" shall mean one or a series of controlled pivotal studies of a specific Program Compound by administration of such Program Compound to human beings where the principal purpose of such trial is to provide confirmatory safety and efficacy data necessary to support the filing for Regulatory Approval of a Product.

1.37 "Preclinical Programs" shall mean the following preclinical and clinical programs with potential backup compounds in accordance with Section 4.3(a): the FTI Program, the ED Program and the MMPI Program.

1.38 "Premium Delivery System" shall have the meaning given in paragraph (d) of the definition of Net Sales.

1.39 "Product" shall mean any product containing one or more of the Program Compounds as an active ingredient, alone or in combination with other active ingredients (including any Bundled Product and any Combination Product).

1.40 "Program Compounds" shall mean (i) the compounds listed on Exhibit 1.40; (ii) the first compound (the selection of which shall be consistent with Abbott using Commercially Reasonable Efforts) from each of the Preclinical Programs to enter Phase I Clinical Trial; (iii) any compounds or products substituted or added by Section 4.3; (iv) all line extensions and formulations of the foregoing; and (v) all analogs, isomers, improvements, derivatives and modifications of the foregoing unless such analog, isomer, improvement, derivative or modification would be considered a new chemical entity and required by the FDA to reenter Phase I Clinical Trial. A compound or product shall be considered a Program Compound regardless of the indication for which it is used.

1.41 "Program Inventions" shall have the meaning given in Section 5.1.

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1.42 "Program Payments" shall have the meaning given in Section 3.1.

1.43 "Program Related Costs" shall mean (i) all direct and indirect costs and expenses that are incurred by Abbott on the Research Program during a given Program Year and allocated in a manner consistent with Abbott's internal, pharmaceutical products division-wide allocation procedures; and (ii) the milestone and license fees paid during a given Program Year or during any extension period of the Program Term by Abbott to (a) Eisai Co. Ltd. (not to exceed Eighteen Million Dollars (\$18,000,000) in the aggregate with respect to the Program Compound known as ABT-751 pursuant to the Eisai Agreement) and (b) Wakunaga Pharmaceutical Co., Ltd. (not to exceed Twenty Seven Million Five Hundred Thousand Dollars (\$27,500,000) in the aggregate with respect to the Program Compound known as ABT-492 pursuant to the Wakunaga Agreement). Any payments made by Abbott to John Hancock pursuant to Sections 6.2 and 6.3(a), (b), (c), (d) and (e) shall constitute Program Related Costs. Any payment made by Abbott to John Hancock pursuant to Section 6.3(f) shall not constitute Program Related Costs. Set forth on Exhibit 1.43 is an example of the calculation of Program Related Costs for a particular Program Compound.

1.44 "Program Term" shall mean a period of four (4) consecutive Program Years.

1.45 "Program Year" shall mean a period of twelve (12) consecutive calendar months commencing on January 1 of each year, except that the first Program Year shall commence on the Execution Date and end on December 31, 2001.

1.46 "Quarterly Reporting Period" shall mean the calendar quarter with respect to the U.S. Territory together with the fiscal quarter ending on the final day of February, May, August and November (as the case may be) with respect to the International Territory. For example, the Quarterly Reporting Period that comprises the second calendar quarter with respect to the U.S. Territory also includes the period from March 1 through May 31 with respect to the International Territory. If Abbott adopts the calendar year as its fiscal year for the International Territory, then the Quarterly Reporting Period for the International Territory shall also be the calendar quarter.

1.47 "Research Program" shall mean all of Abbott's, its Affiliates' and Subcontractors' activities directed towards obtaining Regulatory Approval for the Products, including research, development, safety and efficacy studies, clinical trials, process development, formulation work, regulatory, quality, data collection and analysis and project management.

1.48 "Regulatory Approval" shall mean: (i) with respect to the U.S. Territory, the receipt of approval from the FDA to market a Product in the U.S. Territory; and (ii) with respect to any country in the International Territory, receipt of the governmental approvals required to market a Product in such country, including any pricing and reimbursement authorization required in such country.

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1.49 "Replacement Compound" shall mean a compound (i) made available to Abbott as a result of any transaction involving Abbott or its Affiliates (whether by merger, acquisition or sale of assets or equity, or by license or otherwise), (ii) used for the same class of indications as the Ceased Compound (for example, anti-infectives, cancer, cardiovascular or pain), and (iii) having at least the current and projected potential commercial value to John Hancock as the Ceased Compound.

1.50 "Royalty Term" shall mean, with respect to each Product in each country, a period of ten (10) years from the later of (x) the date of First Commercial Sale of such Product in such country and (y) the two year anniversary of the Execution Date; provided that (i) the obligation to make royalty payments on the Product shall not begin until the two-year anniversary of the Execution Date (and only with respect to Net Sales occurring on or after such date) and (ii) Abbott's obligation to make royalty payments shall cease on December 31, 2015.

1.51 "Subcontractor" shall have the meaning given in Section 2.4.

1.52 "Taisho Agreement" shall mean the Co-Development Agreement dated September 30, 1997 between Taisho Pharmaceutical Co., Ltd. and Abbott related to the Program Compound known as ABT-773.

1.53 "Territory" shall mean both the U.S. Territory and the International Territory, excluding the Eisai Territory with respect to the Program Compound known as ABT-751.

1.54 "U.S. Territory" shall mean the United States of America, excluding Puerto Rico and the U.S. Virgin Islands.

1.55 "Wakunaga Agreement" shall mean the License Agreement dated December 1, 1999 between Wakunaga Pharmaceutical Co., Ltd. and Abbott related to the Program Compound known as ABT-492.

## ARTICLE 2 ANNUAL RESEARCH PROGRAM

2.1 Research Program Term. The Research Program shall be conducted by Abbott during the Program Term, and beyond the Program Term until Abbott either abandons development in accordance with the terms hereof or receives Regulatory Approval for each Program Compound, or some combination thereof.

2.2 Research Plan. The Research Program shall be conducted by Abbott in each Program Year in accordance with the Annual Research Plan for such Program Year. The Annual Research Plan will be provided to John Hancock until Abbott either abandons development in accordance with the terms hereof, or receives Regulatory Approval for, each Program Compound in the U.S. Territory, or some combination thereof. The Annual Research Plan shall be prepared

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by Abbott and presented to John Hancock at least forty-five (45) days prior to the start of each Program Year. The first Annual Research Plan is attached as Exhibit 1.6. Abbott may modify the Annual Research Plan from time to time in order to best meet the objectives of the Research Program. Any such modifications to the Annual Research Plan shall be promptly provided to John Hancock. In addition, Abbott shall provide an Annual Research Plan for each year after the end of the Program Term as long as there is an active research program for any Program Compounds.

2.3 Conduct of Research. Abbott shall use Commercially Reasonable Efforts to conduct the Research Program in good scientific manner and using good laboratory practices, to achieve the objectives of the Research Program efficiently and expeditiously and to comply with all applicable laws and regulations. Notwithstanding anything in this Agreement to the contrary, Abbott does not represent, warrant or guarantee that the Research Program will be successful in whole or in part or result in the registration or commercialization of any pharmaceutical products or that any Products obtaining Regulatory Approval will be a commercial success.

2.4 Subcontracting Research. Abbott may subcontract or outsource to Affiliates or third persons (each, a "Subcontractor") any portion of the Annual Research Plan. Consistent with Abbott's past practices, each Subcontractor shall enter into a confidentiality agreement with Abbott and agreements pursuant to which such Subcontractor is required to comply with all applicable laws and regulations, including conducting the Research Program in good scientific manner and using good laboratory practices, with respect to its work on the Research Program. Abbott shall supervise and be responsible under this Agreement for the work of each such Subcontractor on the Research Program and no subcontracting or outsourcing shall relieve Abbott of any of its obligations hereunder.

2.5 Research Reports and Records. Abbott shall, no later than thirty (30) days before the last day of each Program Year, provide John Hancock with a reasonably detailed report setting forth the status of the Research Program and all Program Related Costs expended by Abbott during such Program Year. The Program Related Costs set forth in such report may include good faith estimates with respect to the last three (3) months of the Program Year, provided that the report under this Section 2.5 for the following Program Year contains the actual Program Related Costs for that three (3) month period. Such report shall also contain such other information related thereto as John Hancock may reasonably request from time to time. Abbott shall, and shall cause each Subcontractor to, maintain complete and accurate records, in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes and for purposes of demonstrating compliance with the terms hereof, that fully and properly reflect all work done, results achieved and Program Related Costs expended in performance of the Research Program. The books and records of Abbott and each Subcontractor related to the Research Program, including, without limitation, those related to the expenditure of Program Related Costs, shall be subject to copying, inspection and audit by (and at the expense of) John Hancock at any time and from time to time. Such audit shall occur upon reasonable notice and during normal business hours by an independent auditor selected by John Hancock and reasonably acceptable to Abbott. John Hancock and its independent auditor shall maintain such

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records and information of Abbott in confidence in accordance with Article 10 and shall not use such records or information except to the extent permitted by this Agreement, including any enforcement of the provisions hereof. In the event that such audit reveals any material breach of Abbott's responsibilities hereunder, Abbott shall (i) pay the reasonable fees and expenses charged by such auditor, and (ii) fully and promptly cure such breach.

### ARTICLE 3 RESEARCH FUNDING

3.1 John Hancock Program Payments. John Hancock shall make the following installment payments on the applicable payment date (the "Payment Date"), for the applicable Program Year, to Abbott to help support the Research Program (the "Program Payments"):

<u>Payment Date</u>	<u>Amount</u>	<u>Program Year</u>
December 1, 2001	\$50,000,000	First
December 1, 2002	\$54,000,000	Second
December 1, 2003	\$58,000,000	Third
December 1, 2004	\$52,000,000	Fourth

All Program Payments shall be expended by Abbott on Program Related Costs and for no other purpose. If John Hancock has not received at least thirty (30) days prior to the Payment Date both (i) the Annual Research Plan for such year and (ii) the report described in Section 2.5 for the previous Program Year, then John Hancock's obligation to make the Program Payment due on such Payment Date shall be suspended until thirty (30) days have elapsed from the date of John Hancock's receipt of both such Annual Research Plan and report.

3.2 Abbott Funding Obligation. Abbott shall spend on Program Related Costs: (i) during each Program Year, at least the Annual Minimum Spending Target for such Program Year and (ii) at least the Aggregate Spending Target during the Program Term. John Hancock's sole and exclusive remedies for Abbott's failure to fund the Research Program in accordance with this Section 3.2 (but not for any other breach of Abbott's other obligations hereunder) are set forth in Sections 3.3 and 3.4.

3.3 Carryover Provisions. Abbott shall be permitted to change its funding obligations under Section 3.2 only as follows:

- (a) If in any Program Year Abbott spends on Program Related Costs, the full amount of the Program Payment provided by John Hancock for such Program Year, but does not spend the full amount of the Annual Minimum Spending Target for such Program Year (including any Annual Carryover Amounts from any prior Program Years), Abbott will spend on Program Related Costs the difference between its expenditure on Program Related Costs for such Program Year and the Annual Minimum Spending Target



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for such Program Year (the "Annual Carryover Amount") in the subsequent Program Year. John Hancock's obligation to make any Program Payment for such subsequent Program Year, if any, pursuant to Section 3.1, shall be deferred until the time that Abbott has spent and notifies John Hancock that it has spent the Annual Carryover Amount in such subsequent Program Year; and

- (b) If Abbott does not expend on Program Related Costs the full amount of the Aggregate Spending Target during the Program Term, Abbott will expend the difference between its expenditures for Program Related Costs during the Program Term and the Aggregate Spending Target (the "Aggregate Carryover Amount") on Program Related Costs during the subsequent year commencing immediately after the end of the Program Term. If Abbott does not spend the Aggregate Carryover Amount on Program Related Costs during such subsequent year, Abbott will pay to John Hancock one-third of the Aggregate Carryover Amount that remains unspent by Abbott, within thirty (30) days after the end of such subsequent year.

3.4 Termination of John Hancock's Program Payment Obligation. If Abbott: (i) abandons development of all Preclinical Programs and Program Compounds in any Program Year during the Program Term (it being understood that such abandonment need not occur entirely in one Program Year); (ii) does not expend on Program Related Costs during any Program Year the full amount of the Program Payment made by John Hancock for such Program Year; (iii) does not reasonably demonstrate in its Annual Research Plan, its intent and reasonable expectation to expend on Program Related Costs during the next Program Year an amount in excess of the Program Payment to be provided by John Hancock for such year; or (iv) does not reasonably demonstrate in its Annual Research Plan its intent and reasonable expectation to expend on Program Related Costs during the Program Term an amount in excess of the Aggregate Spending Target, John Hancock's obligation to make any remaining Program Payments for any succeeding Program Years pursuant to Section 3.1 shall terminate. For the avoidance of doubt, the Program Payments for the Program Year in which such event occurs shall still be due and payable, adjusted only as set forth in the next sentence, if applicable. In addition, in the case of either (i) or (ii) above, Abbott shall (not later than the 10th day following such event) pay to John Hancock (x) the amount, if any, by which the Program Payment made by John Hancock for such year (in the case of (i) above meaning the Program Year in which all Preclinical Programs and Program Compounds were finally abandoned), if any, exceeds one-half of the Program Related Costs actually spent by Abbott during that Program Year and (y) such additional amount that, after giving effect to the payments referred to in this sentence, causes the Program Related Costs for all years in the Program Term to date to have been funded one-third (1/3) by John Hancock and two-thirds (2/3) by Abbott.

3.5 Hancock Funding Obligation. John Hancock's entire obligation hereunder shall be limited to providing the Program Payments set forth in Section 3.1. Abbott shall be solely

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responsible for funding all Program Related Costs in excess of the Program Payments from John Hancock.

#### ARTICLE 4 PRODUCT RESEARCH AND DEVELOPMENT

4.1 Commercially Reasonable Efforts. Abbott shall be solely responsible for the clinical development, government approval, manufacturing, marketing, sales and distribution of Products. Abbott will use, and will cause each of its Affiliates and Licensees to use, Commercially Reasonable Efforts to pursue the clinical development, government approval, manufacturing, marketing, sales and distribution of Products throughout the Territory. The obligations of Abbott, its Affiliates and Licensees with respect to any Product under this Article 4 are expressly conditioned upon the safety, efficacy and commercial feasibility of each Product, consistent with using Commercially Reasonable Efforts, but no license, assignment or other transfer of rights by Abbott will modify or reduce Abbott's obligations hereunder (except as set forth in Article 14). It is the parties' expectation that under normal circumstances Abbott will file for Regulatory Approval with respect to each Product in Europe within two (2) years from the date of the NDA filing for such Product in the U.S. Territory and in Japan within five (5) years from such NDA filing date; provided, however, that these time frames may be extended or otherwise altered based upon unforeseen circumstances that legitimately impact such regulatory filings in such foreign jurisdictions.

4.2 Marketing and Sale Responsibility. Without limiting the generality of Section 4.1, within six (6) months of obtaining Regulatory Approval for a Product in a given country, Abbott, its Affiliates or Licensees shall commence to market and sell such Product in such country. Abbott's obligation to market and sell a Product shall not apply to a Product in any country if Abbott has not commenced or has ceased marketing and selling such Product in such country substantially on account of adverse business or financial conditions caused by the regulatory authorities or other governmental authorities of such country (including not commencing marketing and selling in a country where the regulatory authorities have price or reimbursement approval and the price or reimbursement approval or that proposed by the regulatory authorities or government authorities is unacceptable to Abbott) which causes the marketing and sale of such Product in such country to be contrary to the financial best interests of John Hancock and Abbott; provided, however, that Abbott, its Affiliates or Licensees shall commence or resume marketing and sale of such Product in such country as soon as reasonably practical after such adverse business or financial conditions cease to exist.

4.3 Failure of Program Compound to Progress.

- (a) Preclinical Programs: ED Program, FTI Program and MMPI Program.  
With respect to any Program Compound resulting from a Preclinical Program that Abbott ceases to develop past Phase I Clinical Trial (i.e., does not enter a Phase II Clinical Trial) (a "Failed Early Stage Program

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Compound"), for which Abbott or its Affiliates has or will have one or more other compounds in such respective Preclinical Program (which includes all in-licensed compounds not yet approved for marketing), the next compound to enter Phase I Clinical Trials from such Preclinical Program shall be considered a Program Compound in all respects hereunder, as of the date of the cessation of such Failed Early Stage Program Compound; provided however, with respect to each Preclinical Program, there shall be no more than three Program Compounds substituted under this Section 4.3(a) (for an aggregate maximum of nine (9) such substitutions for all Preclinical Programs). At the time a Preclinical Program becomes a Ceased Program, Abbott shall have no further obligation to provide a substitute for a Failed Early Stage Program Compound.

- (b) Failure of ABT-492 or ABT-510 to Yield a Compound that Enters a Phase II Clinical Trial. If (i) ABT-492 fails to enter a Phase II Clinical Trial, or (ii) ABT-510 fails to enter a Phase II Clinical Trial, then within six (6) months after the failure of the first such Program Compound to enter a Phase II Clinical Trial, Abbott shall substitute a compound in a Phase II Clinical Trial having a commercial value not less than that currently expected for ABT-492 and ABT-510, respectively (as of the date of execution of this Agreement).
- (c) Cessation as a Result of an Acquired Replacement Compound. If Abbott ceases or substantially ceases developing, marketing or selling any Program Compound (that is in Phase I or beyond) or Product (a "Ceased Compound"), and if such cessation or substantial cessation is a result of Abbott's acquisition of a Replacement Compound, then the Replacement Compound shall be considered a Program Compound and/or Product from the date of such acquisition and the Ceased Compound shall no longer be considered a Program Compound.

In the event that the Replacement Compound has been approved for marketing by the FDA and the Ceased Compound has not been approved for marketing by the FDA as of the date of such acquisition, Section 4.3(d) shall apply and the first paragraph of this Section 4.3(c) shall not apply.

In the event that the Ceased Compound has been approved for marketing by the FDA as of the date of such acquisition, John Hancock shall have the option, in its sole discretion, to have Abbott maximize the commercial value of the Ceased Compound pursuant to Section 4.3(d) instead of having the Ceased Compound be subject to this Section 4.3(c).

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- (d) Cessation for Reasons Other than Section 4.3(c). If a Program Compound (that is in Phase I or beyond) or Product becomes a Ceased Compound for any reason not as a result of the acquisition of a Replacement Compound as set forth in Section 4.3(c) above and provided that such Ceased Compound has commercial value, then
- (i) as soon as is practicable Abbott shall maximize the commercial value, if any, of the Ceased Compound to both parties by out-licensing or divesting such Ceased Compound to a third party; provided, however, if the out-licensing or divestiture of such Ceased Compound requires the approval of Taisho Pharmaceutical Co., Ltd. (in the case of Program Compound ABT-773), Eisai Co., Ltd. (in the case of Program Compound ABT-751) or Wakunaga Pharmaceutical Co., Ltd. (in the case of Program Compound ABT-492), pursuant to the respective In-License Agreement, and such entity does not grant such approval, then Abbott shall within a reasonable period of time but not more than three months substitute a compound (which shall thereupon become a "Program Compound") having at least the current and projected potential commercial value as such Ceased Compound;
  - (ii) John Hancock shall be permitted (but have no obligation) to assist in such out-license and/or divestiture effort; and
  - (iii) Abbott shall remunerate John Hancock based on the sales of such Ceased Compound by the third party that has acquired or licensed the Ceased Compound (the "Acquirer") in a manner most consistent with the allocation that would have applied hereunder had such Ceased Compound not been so out-licensed or divested, i.e., in accordance with the royalties and milestones payable hereunder. The appropriate royalty rate payable to John Hancock shall be determined by adding the Acquirer's Net Sales of the Ceased Compound to the total Net Sales of other Products.
- (e) Divestiture. Notwithstanding anything herein to the contrary, Abbott shall not divest or out-license any Program Compound (which shall mean a sale, license or other transfer by Abbott of the right to develop, market and sell any Product containing such Program Compound either (i) in all of North America or (ii) in the countries of Japan and/or the European Union that have at least two-thirds of the total population of Japan and the European Union), without John Hancock's prior written consent, which consent shall not be unreasonably withheld; provided however, if such Program Compound is being divested as a result of direction from the

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Federal Trade Commission to so divest, John Hancock's written consent shall not be required.

- (f) Notice and Information. Abbott shall promptly notify John Hancock upon occurrence of any decision by Abbott to cease or substantially cease developing, marketing or selling any Program Compound or Product. In addition, Abbott shall provide to John Hancock all information reasonably requested by John Hancock related to any Replacement Compound, Program Compound, or Product that is subject to the provisions of this Section 4.3.
- (g) Commercially Reasonable Efforts. Nothing in this Section 4.3 shall lessen any of Abbott's other obligations under this Agreement nor permit Abbott to perform in any manner that is not clearly consistent with using its Commercially Reasonable Efforts hereunder.

4.4 Arm's-Length. Abbott shall not research, develop, manufacture, market, sell, distribute, out-license or otherwise treat any Program Compounds or Products differently, as compared to any other Abbott compounds or products, on account of any of John Hancock's rights hereunder. Furthermore, all distribution agreements, licenses, out-licenses and other agreements relating to the research, development, manufacturing, marketing, sale, distribution, licensing, out-licensing or divestiture of and all other transactions involving any Program Compounds or Products to or with any third party (except to Abbott's Affiliates) shall be on arm's-length terms and conditions.

4.5 In-License Agreements. Abbott shall comply in all material respects with the terms and conditions of the In-License Agreements. Abbott shall not amend the In-License Agreements or waive any of its rights thereunder without John Hancock's prior written consent (such consent not to be unreasonably withheld), unless such amendment or waiver does not have and would not have a material adverse effect on John Hancock's interests hereunder. To the extent that Abbott or any of its Affiliates obtains the right to market, distribute or sell Products containing the Program Compound known as ABT-751 in the Eisai Territory, then sales by Abbott, its Affiliates and Licensees of such Products in such territory shall be included in all respects hereunder (including without limitation in Net Sales and the Territory).

## ARTICLE 5 PROGRAM INVENTIONS

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5.1 Ownership. As between Abbott and John Hancock, all inventions, innovations, ideas, discoveries, technology, know-how, methods, data, applications and products (in each case whether or not patentable) arising from the Research Program or otherwise related to the Program Compounds (collectively, the "Program Inventions") shall be exclusively owned by or assigned to Abbott. Abbott shall not divest, out-license or otherwise transfer any of its right, title

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or interest in or to any Program Inventions which would prevent or impair Abbott's ability to fulfill its obligations to John Hancock under this Agreement.

5.2 Patent Prosecution and Maintenance. To the extent it owns a Program Invention or has the contractual right to pursue patent protection for a Program Invention, Abbott will use Commercially Reasonable Efforts to obtain patent protection for the Program Inventions in the Territory. As between Abbott and John Hancock, Abbott shall be responsible for all costs and expenses and control all decisions related to pursuing such patent protection, including the preparation, filing (foreign and/or domestic), prosecution, issuance and maintenance of patent applications or patents covering Program Inventions.

5.3 Enforcement. As between Abbott and John Hancock, Abbott shall have the sole right and authority to enforce the patents or any other rights arising from the Program Inventions (including without limitation the Patents) against any infringers. If Abbott initiates any action or lawsuit to enforce such patents or other rights, it shall be solely responsible for the cost and expense thereof. Abbott will promptly notify John Hancock at such time as it becomes aware of any infringement activities and of any such enforcement actions or lawsuit, and Abbott will provide information concerning them as reasonably requested by John Hancock. All moneys recovered upon the final judgment or settlement of any such action or lawsuit, less the out-of-pocket cost and expense thereof, shall be allocated between Abbott and John Hancock proportional to Abbott's lost profits and John Hancock's lost royalties as a result of such infringement.

## ARTICLE 6 MILESTONE PAYMENTS TO JOHN HANCOCK

6.1 [Intentionally omitted].

6.2 Management Fee. On December 1, 2002, 2003 and 2004, Abbott shall pay to John Hancock a management fee, each of which shall be in the amount of Two Million Dollars (\$2,000,000).

6.3 Milestone Notification and Payments. Abbott shall promptly notify John Hancock of the occurrence any of the following events that give rise to Abbott's obligation to make a payment pursuant to this Section 6.3 (each, a "Milestone Payment"). Except as hereinafter limited, Abbott shall pay the following Milestone Payments to John Hancock in the amounts and at the times set forth below with respect to each Program Compound:

- (a) One Million Dollars (\$1,000,000) shall be paid within thirty (30) days after the allowance by the FDA of each Investigational New Drug Application for such Program Compound;

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- (b) Two Million Dollars (\$2,000,000) shall be paid within thirty (30) days after the initiation of each Phase I Clinical Trial with such Program Compound;
- (c) Three Million Dollars (\$3,000,000) shall be paid within thirty (30) days after the initiation of each Phase II Clinical Trial with such Program Compound;
- (d) Four Million Dollars (\$4,000,000) shall be paid within thirty (30) days after the initiation of each Phase III Clinical Trial with such Program Compound; and
- (e) Five Million Dollars (\$5,000,000) shall be paid within thirty (30) days after the filing of each NDA with the FDA for such Program Compound.

In addition, except as hereinafter limited, Abbott shall pay the following Milestone Payments to John Hancock in the amounts and at the times set forth below:

- (f) (i) Twenty Million Dollars (\$20,000,000) shall be paid within thirty (30) days after the Regulatory Approval of the first Product in the U.S. Territory;
- (ii) Ten Million Dollars (\$10,000,000) shall be paid within thirty (30) days after the Regulatory Approval of the second Product in the U.S. Territory; and
- (iii) Ten Million Dollars (\$10,000,000) shall be paid within thirty (30) days after the Regulatory Approval of third Product in the U.S. Territory.

The aggregate of Milestone Payments under Section 6.3(a), (b), (c), (d), and (e) for all Program Compounds shall be limited to Eight Million Dollars (\$8,000,000), and once such aggregate limit has been paid, no further payments shall be due and payable under Sections 6.3(a), (b), (c), (d) or (e).

The aggregate of Milestone Payments under Sections 6.3(a), (b), (c), (d) and (e) for all Program Compounds shall be limited to zero dollars (\$0) during the first Program Year, Two Million Dollars (\$2,000,000) during the second Program Year, and Six Million Dollars (\$6,000,000) during the third Program Year, and once such annual limit has been reached for these particular Program Years, no further payments shall be due under Sections 6.3(a), (b), (c), (d) and (e) for the remainder of such Program Year; provided that any amounts that would have been due to John Hancock but for such annual limits shall be paid in subsequent Program Years so long as the Program Compound to which it relates has not been abandoned, divested or out-licensed by Abbott, subject to the Eight Million Dollar (\$8,000,000) limitation set forth above. Subject to

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the limitations above, the Milestone Payments under Sections 6.3(a), (b), (c), (d) and (e) may be made more than once with respect to each Program Compound.

The aggregate of Milestone Payments under Section 6.3(f) for all Program Compounds shall be limited to Forty Million Dollars (\$40,000,000), and once such aggregate limit has been paid, no further payments shall be due and payable under Section 6.3(f). In addition, Milestone Payments under Section 6.3(f) shall not be paid more than once for any particular Program Compound.

Exhibit 1.40 sets forth the current stage of clinical development for each Program Compound.

## ARTICLE 7 ROYALTIES

7.1 Royalty Rates. Subject to the limitation set forth below, Abbott shall pay to John Hancock royalties equal to the following percentages of Net Sales, aggregated on a yearly basis, of all Products in the Territory:

<u>Royalty percentage</u>	<u>Yearly Net Sales (in millions) of all Products in the Territory</u>
8.5% of those Net Sales	up to \$400
and then 4% of those Net Sales	in excess of \$400 up to \$1,000
and then 1% of those Net Sales	in excess of \$1,000 up to \$2,000
and then 0.5% of those Net Sales	in excess of \$2,000

Net Sales shall be aggregated yearly (i) in the case of the U.S. Territory, on a calendar year basis, together with (ii) in the case of the International Territory, on a December 1 to November 30 basis, in each case consistent with the determination of Quarterly Reporting Periods.

7.2 Royalty Term. The duration of the obligation to make royalty payments on each Product shall be determined on a country-by-country basis and shall last for the duration of the Royalty Term in each given country for such Product.

## ARTICLE 8 ROYALTY REPORTS AND ACCOUNTING

8.1 Reports, Exchange Rates. With respect to every Quarterly Reporting Period for which Abbott is obligated to pay any royalty hereunder, Abbott shall furnish to John Hancock a single written report for such Quarterly Reporting Period within sixty (60) days after the end of such Quarterly Reporting Period (that is, within sixty (60) days after each March 31, June 30, September 30 and December 31, as the case may be) showing in reasonably specific detail:

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- (a) the total gross sales in each country for each Product sold by Abbott, its Affiliates and Licensees in the Territory and the detailed calculation of Net Sales from gross sales in each country for each Product;
- (b) the royalties payable in Dollars, if any, which shall have accrued hereunder;
- (c) the dates of the First Commercial Sale of each Product in any country in the Territory during such Quarterly Reporting Period; and
- (d) the exchange rates used in determining the amount of Dollars.

With respect to sales of Products invoiced in Dollars, the gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same), and royalties payable shall be expressed in Dollars. With respect to sales of Products invoiced in a currency other than Dollars, the gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same) and royalties payable shall be expressed in their Dollar equivalent, calculated using the Inter Bank rate set forth in the International Report published by International Reports Inc. as Foreign Exchange Rates quoted in New York on the day nearest the last business day of the Quarterly Reporting Period.

## 8.2 Audits.

- (a) Upon the written request of John Hancock and, in the absence of any breach by Abbott hereunder, not more than once in each calendar year, Abbott shall permit John Hancock and an independent certified public accounting firm of nationally recognized standing, selected by John Hancock and reasonably acceptable to Abbott, at John Hancock's expense, to have access during normal business hours to such of the records of Abbott, its Affiliates and Licensees to verify the accuracy of the royalty reports and the amounts and calculation of any payments required hereunder for any year ending not more than five (5) years prior to the date of such request.
- (b) If such accounting firm concludes that additional royalties or other payments were owed during such period, Abbott shall have the option to invoke the proceedings of Section 16.7 below or pay the additional royalties or other payments within thirty (30) days after the date John Hancock delivers to Abbott such accounting firm's written report so concluding. The reasonable fees and expenses charged by such accounting firm shall be paid by John Hancock; provided, however, if the audit discloses that the amounts payable by Abbott for any Quarterly Reporting Period are more than one hundred five percent (105%) of the royalties

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actually paid for such period, then Abbott shall pay the reasonable fees and expenses charged by such accounting firm.

- (c) Abbott shall cause its Affiliates to, and shall include in each license granted by it relating to a Program Compound or Product a provision requiring the Licensee to, (i) make reports to Abbott, (ii) keep and maintain records of Net Sales made pursuant to such license and (iii) grant access to such records by John Hancock and its accounting firm or other auditor to the same extent required of Abbott under this Agreement.
- (d) All reports and payments not disputed as to correctness by John Hancock within five (5) years after receipt thereof shall thereafter conclusively be deemed correct for all purposes, and Abbott, its Affiliates and Licensees shall be released from any liability or accountability with respect to such reports and payments.

8.3 Confidential Financial Information. John Hancock shall treat all information subject to review under this Article 8, and shall cause its accounting firm to agree to treat all such information, in accordance with the provisions of Article 10.

8.4 Accounting Principles. All accounting hereunder, including without limitation all determinations of gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same), Program Related Costs and all calculations underlying such determinations, shall be made in accordance with generally accepted accounting principles as in effect in the United States, consistently applied.

## ARTICLE 9 PAYMENTS

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9.1 Payment Terms. With respect to every Quarterly Reporting Period for which Abbott is obligated to pay a royalty hereunder, such royalties shall be due and payable in a single payment within sixty (60) days of the end of such Quarterly Reporting Period (that is, within sixty (60) days of each March 31, June 30, September 30 and December 31, as the case may be). Payment of royalties may be made in advance of such due date.

9.2 Payment Method. All royalties and other payments by Abbott to John Hancock under this Agreement shall be made by bank wire transfer in immediately available funds in accordance with the instructions set forth on Exhibit 9.2 attached hereto or in accordance with such other instructions as John Hancock may give from time to time.

9.3 Late Payments. Each party shall pay interest to the other on the aggregate amount of any payments by it that are not paid on or before the date such payments are due under this Agreement, including, without limitation, any disputed payments or payments resulting from any



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audit, at a rate per annum equal to the lesser of (a) the prime rate of interest plus two hundred (200) basis points as reported by Citibank, N.A. in New York, from time to time (with any change in such reported rate being effective immediately for purposes hereof), or (b) the highest rate permitted by applicable law, calculated on the number of days such payments is delinquent until paid in full in cash. All such amounts shall be payable upon demand.

## ARTICLE 10 CONFIDENTIALITY

10.1 Nondisclosure Obligations. Except as otherwise provided in this Article 10, during the term of the Agreement and for a period of ten (10) years thereafter, (a) John Hancock shall maintain in confidence in accordance with such procedures as are adopted by John Hancock to protect its own confidential information and shall use only for purposes of this Agreement (including, without limitation, enforcement of the terms hereof), information and data related to the Program Compounds or Products; and (b) John Hancock shall also maintain in confidence in accordance with such policies, and use only for purposes of this Agreement, all information and data supplied by Abbott under this Agreement, which if disclosed in writing is marked "confidential", if disclosed orally is promptly thereafter summarized and confirmed in writing to the other party and marked "confidential", or if disclosed in some other form is marked "confidential."

10.2 Permitted Disclosures. For purposes of this Article 10, information and data described in clause (a) or (b) above shall be referred to as "Confidential Information". John Hancock may disclose Confidential Information as required by applicable law, regulation or judicial process, provided that John Hancock shall, if legally permitted, give Abbott prompt written notice thereof. The obligation not to disclose or use Confidential Information shall not apply to any part of such Confidential Information that (i) is or becomes patented, published or otherwise part of the public domain other than by acts or omissions of John Hancock in contravention of this Agreement; or (ii) is disclosed to John Hancock by a third party, provided such Confidential Information was not obtained on a confidential basis by such third party from Abbott, its Affiliates or Licensees; or (iii) prior to disclosure under the Agreement, was already in the possession of John Hancock, provided such Confidential Information was not obtained directly or indirectly from Abbott, its Affiliates or Licensees under an ongoing obligation of confidentiality; or (iv) is disclosed in a press release agreed to by both parties under Section 10.3 below.

10.3 Publicity Review. Without the prior written consent of the other party, neither party shall make any statement to the public regarding the execution and/or any other aspect of the subject matter of this Agreement and John Hancock shall not make any statement to the public regarding any work under the Research Program; provided that, Abbott may make statements to the public regarding work done under the Research Program (without reference to or mention of John Hancock) and the commercialization of any Products resulting therefrom in accordance with its standard business practices. John Hancock and Abbott shall not disclose any

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terms or conditions of this Agreement to any third party without the prior consent of the other party, except as set forth above in this Section 10.3 or as required by applicable law, regulation or court order. The parties agree not to issue a press release announcing the execution of this Agreement.

## ARTICLE 11 TERM AND TERMINATION

11.1 Expiration. This Agreement shall expire upon satisfaction of Abbott's obligations to pay royalties under Section 7.2 and all other amounts under this Agreement.

11.2 Termination; Material Breach. It is the parties' express intent that consideration shall be given to remedying any breach of this Agreement through the payment of monetary damages or such other legal or equitable remedies as shall be appropriate under the circumstances and that there shall only be a limited right to terminate this Agreement under the following circumstances.

- (a) In the event that the court, in accordance with the procedures set forth in Section 16.2, has issued a ruling that John Hancock has breached its obligation under Section 3.1 of this Agreement (obligation to make payments), and such ruling specified the actions to be taken by John Hancock on account of such breach, and John Hancock has failed to comply with the terms of such ruling within the time period specified therein for compliance and the time for any appeal has expired without the submission of an appeal, then, in addition to all other rights available to Abbott under law and equity, including its right to enforce such ruling in court, Abbott shall have the right to terminate the Agreement as a result of John Hancock's failure to abide by the terms of this Agreement and such ruling.
- (b) In the event that the court, in accordance with the procedures set forth in Section 16.2, has issued a ruling that Abbott has breached a material obligation under this Agreement, and such ruling specified the actions to be taken by Abbott on account of such breach, and Abbott has failed to comply with the terms of such ruling within the time period specified therein for compliance and the time for any appeal has expired without the submission of an appeal, then, in addition to all other rights available to John Hancock under law and equity, including its right to enforce such ruling in court, John Hancock shall have the right to terminate the Agreement, each as a result of Abbott's failure to abide by the terms of this Agreement and such ruling.

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**JH 008103**

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11.3 Effect of Expiration or Termination. Expiration or, if applicable, termination of this Agreement shall not relieve the parties of any obligation accruing prior to such expiration or termination. The provisions of Articles 8 (Royalty Reports and Accounting), 10 (Confidentiality), 11 (Term and Termination), 12 (Warranties and Indemnification) and 16 (Miscellaneous) shall survive the expiration or termination of this Agreement.

## ARTICLE 12 WARRANTIES AND INDEMNITY

12.1 John Hancock Representations and Warranties. John Hancock represents and warrants to Abbott that as of the Execution Date:

- (a) The execution and delivery of this Agreement and the performance of the transactions contemplated hereby have been duly authorized by all appropriate John Hancock corporate action. This Agreement constitutes John Hancock's valid and binding legal obligation, enforceable against it in accordance with its terms.
- (b) The performance by John Hancock of any of the terms and conditions of this Agreement on its part to be performed does not and will not constitute a breach or violation of its organizational documents or any other material agreement or understanding, written or oral, to which it is a party or any law, statute, rule or regulation by which it is bound.
- (c) No consent, approval, license or authorization of, or designation, declaration or filing with, any court or governmental authority is or will be required on the part of John Hancock in connection with the execution, delivery and performance by John Hancock of this Agreement or any other agreements or instruments executed and delivered by John Hancock in connection herewith or therewith, including, without limitation, any filings pursuant to federal or state securities laws or pursuant to any federal anti-trust laws.
- (d) Neither John Hancock nor any person acting on its behalf (i) has taken or will take any action which would subject this Agreement and the consummation of the transactions contemplated hereby to the registration or qualification requirements of any federal or state securities laws, (ii) has dealt with any broker, finder or other similar person in connection with the transactions contemplated by this Agreement or (iii) is under any obligation to pay any broker's fee, finder's fee or commission in connection with such transactions.

12.2 Abbott Representations and Warranties. Abbott represents and warrants to John Hancock that as of the Execution Date:

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- (a) The execution and delivery of this Agreement and the performance of the transactions contemplated hereby have been duly authorized by all appropriate Abbott corporate action. This Agreement constitutes Abbott's valid and binding legal obligation, enforceable against it in accordance with its terms.
- (b) The performance by Abbott of any of the terms and conditions of this Agreement on its part to be performed does not and will not constitute a breach or violation of its organizational documents or any other agreement or understanding, written or oral, to which it is a party or any law, statute, rule or regulation by which it is bound.
- (c) No consent, approval, license or authorization of, or designation, declaration or filing with, any court or governmental authority is or will be required on the part of Abbott in connection with the execution, delivery and performance by Abbott of this Agreement or any other agreements or instruments executed and delivered by Abbott in connection herewith or therewith, including, without limitation, any filings pursuant to federal or state securities laws or pursuant to any federal anti-trust laws, except those consents, approvals, licenses, authorizations, and other requirements imposed by governmental authorities (both U.S. and foreign) and such declarations and filings with governmental authorities (both U.S. and foreign) required in the normal course of pharmaceutical research, development, marketing and sale.
- (d) Set forth on Exhibit 12.2(d) is the full name, chemical name, detailed description of the stage of development and current status, for each Program Compound. Set forth on Exhibit 1.6 in each Annual Research Plan is a description of projected milestones and dates thereof, projected year of NDA filing, and projected costs to be incurred by Abbott during the Program Term, for each Program Compound. Such projections were prepared in good faith and with due care based on reasonable assumptions, and represent the reasonable estimate of Abbott based on information available as of the date of such projections and as of the date hereof; it being agreed that such projections do not constitute any warranty as to the future performance of the Program Compounds and that actual results may vary from such projections.
- (e) Set forth on Exhibit 12.2(e) is a list and description of all domestic and foreign patents, patent rights, patent applications and all patent applications that are in the process of being prepared that are owned by or registered in the name of Abbott, or of which Abbott is a licensee or in which Abbott has any right, which claim any of the Program Compounds (the "Patents"). Abbott solely owns all of the Patents, except as indicated

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on Exhibit 12.2(e). All of the material Patents have been duly filed in or issued by the United States Patent and Trademark Office or the equivalent foreign patent office identified on Exhibit 12.2(e), as the case may be, and have been properly maintained and renewed in accordance with all applicable laws and regulations. With respect to the Patents that it does not own, Abbott has an exclusive and valid license thereunder to develop, make, have made, use, market and sell (with the right to sublicense) the applicable Program Compounds in the entire Territory; provided however, (i) with respect to Italy, Abbott has such rights that are co-exclusive with Eisai Co. Ltd. for the Program Compound known as ABT-751 and (ii) with respect to Japan, Abbott has such rights that are co-exclusive with Taisho Pharmaceutical Co., Ltd. for the Program Compound known as ABT-773. Except with respect to the Preclinical Programs, to Abbott's knowledge, it is not necessary to obtain or license any patents, patent rights, inventions, copyrights, manufacturing processes, formulae, trade secrets, proprietary rights or know-how that it does not currently have in order to (i) develop, make, have made, use, market and sell the Program Compounds or (ii) conduct the Research Program as heretofore conducted and as proposed to be conducted. Except with respect to those Program Compounds that are the subject of In-License Agreements, the Program Compounds are owned exclusively by Abbott, free and clear of any liens or encumbrances of any other person and, to Abbott's knowledge, Abbott does not require the consent of any other person to develop, make, have made, use, market and sell the Program Compounds.

- (f) Except as set forth in Exhibit 12.2(f) (but in any event, as of the Execution Date, such matters are not, and could not reasonably be expected to be material), Abbott has not received any communications alleging that, and no claim is pending or, to the knowledge of Abbott, threatened to the effect that, the operations of Abbott with respect to the Research Program or the Program Compounds infringe upon or conflict with (or will infringe or conflict with) the asserted rights of any other person under any domestic or foreign patent, trademark, service mark, copyright, trade secret, proprietary right or any other intellectual property right, and, except for the Preclinical Programs, there is no material basis known to Abbott for any such claim (whether or not pending or threatened). No claim is pending or, to the knowledge of Abbott, threatened to the effect that any of the Patents are invalid or unenforceable by Abbott, and there is no material basis known to Abbott for any such claim (whether or not pending or threatened). The publication of any material technical information with respect to the Program Compounds developed by and belonging to Abbott is subject to review and approval under Abbott's existing procedures.
- (g) Except for the In-License Agreements and customary employment and consulting agreements with Abbott's employees and consultants, there are



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no outstanding options, licenses, or agreements of any kind relating to the Patents or any of the Program Compounds or the transactions contemplated by this Agreement, which license the Patents or any technical information developed in the course of the clinical development program to any third party to register, market or sell any of the Program Compounds or Products.

- (h) To the knowledge of Abbott with respect to the Research Program and each of the Program Compounds, Abbott is not now, and in performing its obligations hereunder will not be, in any way making an unlawful or wrongful use of any confidential information, know-how, or trade secrets of any other person.
- (i) Neither this Agreement nor any Exhibit to this Agreement (including the compound reports attached as Exhibit 12.2(i) hereto (the "Compound Reports")) contains any untrue statement of material fact or omits to state any material fact necessary to make the statements contained herein or therein not misleading. There is no fact known to Abbott (other than generally available information concerning the pharmaceutical industry in general) as of the date of this Agreement that has not been disclosed in this Agreement or any Exhibit to this Agreement which has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of the Research Program or any of the Program Compounds.
- (j) Neither Abbott nor any person acting on its behalf (i) has taken or will take any action which would subject this Agreement and the consummation of the transactions contemplated hereby to the registration or qualification requirements of any federal or state securities laws, (ii) has dealt with any broker, finder or other similar person in connection with the transactions contemplated by this Agreement or (iii) is under any obligation to pay any broker's fee, finder's fee or commission in connection with such transactions.
- (k) Other than generally publicized actions, proceedings or investigations concerning the pharmaceutical industry in general, there is no action, proceeding or investigation pending or, to the knowledge of Abbott, threatened which (i) questions the validity of this Agreement or any action taken or to be taken by Abbott pursuant thereto or (ii) which has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of the Research Program or any of the Program Compounds.

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- (l) With respect to the Research Program and each of the Program Compounds, Abbott has (and in the future will have) obtained, to the extent permitted by law, from each of its employees, consultants, Affiliates and Subcontractors an agreement that reasonably protects Abbott's interest in the Program Inventions, Program Compounds and Products.
- (m) With respect to each Program Compound, since the date of its respective Compound Report, to the knowledge of Abbott, no condition, circumstance or fact has arisen (other than generally available information concerning the pharmaceutical industry in general) nor has Abbott made any change in the conduct of the Research Program which, individually or in the aggregate, has resulted in, or could reasonably be expect to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of such Program Compounds.
- (n) Each In-License Agreement is valid, binding and in full force and effect, and there is no event which has occurred or exists, which constitutes or which, with notice and/or the passage of time, would constitute a material default or breach under any such contract by Abbott or, to Abbott's knowledge, any other party thereto, or would cause the acceleration of any obligation of any party thereto or give rise to any right of termination or cancellation thereof. Abbott has no reason to believe that the parties to each In-License Agreement will not fulfill their obligations thereunder in all material respects or that such parties do not have the right to grant the licenses granted thereunder. Abbott has no reason to believe that it will not fulfill its obligations under the In-License Agreements. Under the Eisai Agreement, neither Abbott nor its Affiliates has the right to market, distribute or sell Products containing the Program Compound known as ABT-751 in the Eisai Territory (with the exception of Italy).

12.3 No Conflict. Abbott and John Hancock represent and warrant that this Agreement does not, and will not, conflict with any other right or obligation provided under any other agreement or obligation that Abbott or John Hancock has with or to any third party.

12.4 Compliance with Law. Each party represents and warrants to the other that it will comply with all applicable laws, regulations and guidelines in connection with its performance of its obligations and rights pursuant to this Agreement, including the regulations of the United States and any other relevant nation concerning any export or other transfer of technology, services or products.

12.5 No Other Warranties. EACH PARTY TO THIS AGREEMENT AGREES THAT, EXCEPT FOR THE REPRESENTATIONS AND WARRANTIES CONTAINED IN THIS AGREEMENT, NEITHER PARTY MAKES ANY OTHER REPRESENTATIONS OR

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WARRANTIES, AND EACH HEREBY DISCLAIMS ANY OTHER REPRESENTATIONS OR WARRANTIES MADE BY ITSELF OR ANY OF ITS OFFICERS, DIRECTORS, EMPLOYEES, AGENTS, FINANCIAL AND LEGAL ADVISORS OR OTHER REPRESENTATIVES, WITH RESPECT TO THE EXECUTION AND DELIVERY OF THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED BY THIS AGREEMENT, NOTWITHSTANDING THE DELIVERY OR DISCLOSURE TO THE OTHER OR THE OTHER'S REPRESENTATIVES OF ANY DOCUMENTATION OR OTHER INFORMATION WITH RESPECT TO ANY ONE OR MORE OF THE FOREGOING.

12.6 General Indemnification of John Hancock. Abbott shall indemnify and hold John Hancock and its Affiliates, agents, directors and employees harmless, and hereby forever releases and discharges John Hancock and its Affiliates, agents, directors and employees, from and against all Losses related to or arising out of, directly or indirectly, (i) any negligence, recklessness or intentional misconduct of Abbott or its Affiliates, agents, directors, employees, Subcontractors, licensees (including Licensees) or sublicensees in connection with the Research Program, Program Compounds or Products, or (ii) any manufacture, use, storage, distribution or sale of the Program Compounds or Products by anyone, including without limitation all Losses related to any personal injury or death, or (iii) any breach by Abbott of its representations, warranties or obligations hereunder, or (iv) the consummation of the transactions contemplated hereby, except, in each case, to the extent any such Losses are the result of (A) any breach by John Hancock of its representations, warranties or obligations hereunder, or (B) any negligence, recklessness, or intentional misconduct by John Hancock or its Affiliates, agents, directors, employees.

12.7 Indemnification Relating to Certain In-Licensed Compounds. Abbott shall indemnify and hold John Hancock and its Affiliates, agents, directors and employees harmless, and hereby forever releases and discharges John Hancock and its Affiliates, agents, directors and employees, from and against all Losses to the extent related to or arising out of, directly or indirectly, the fact that Abbott's rights in the Program Compounds known as ABT-773, ABT-492 and ABT-751 and the Patents and other patent rights, copyrights, trade secret rights and other intellectual property rights related thereto arise from the Taisho Agreement, the Wakunaga Agreement or the Eisai Agreement respectively, rather than being owned by Abbott as with the other Program Compounds. Accordingly, by way of example and without limiting the foregoing, Abbott's indemnification obligation under this Section 12.7 will arise upon (i) any impairment of Abbott's ability to perform its obligations under this Agreement in the entire Territory as a result of Abbott's rights to the Program Compounds known as ABT-773, ABT-442 and ABT-751 arising from the Taisho Agreement, Wakunaga Agreement and the Eisai Agreement, respectively or (ii) a breach by Abbott or any other person of any of the In-License Agreements; except, in each case, to the extent any such Losses are the result of (A) any breach by John Hancock of its representations, warranties or obligations hereunder, or (B) any negligence, recklessness, or intentional misconduct by John Hancock or its Affiliates, agents, directors, employees.

12.8 Procedure. If John Hancock or any of its Affiliates, agents, directors or employees (each, an "Indemnitee") intends to claim indemnification under this Article 12, it shall



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promptly notify Abbott (the "Indemnitor") of any Loss or action in respect of which the Indemnatee intends to claim such indemnification, and the Indemnitor shall have the right to participate in, and, to the extent the Indemnitor so desires, to assume the defense thereof with counsel selected by the Indemnitor; provided, however, that an Indemnatee shall have the right to retain its own counsel, with the fees and expenses of such counsel to be paid by the Indemnitor, if representation of such Indemnatee by the counsel retained by the Indemnitor would be inappropriate due to actual or potential differing interests between such Indemnatee and any other party represented by such counsel in such proceedings. The indemnity obligation in this Article 12 shall not apply to amounts paid in settlement of any loss, claim, damage, liability or action if such settlement is effected without the consent of the Indemnitor, which consent shall not be withheld unreasonably or delayed. The failure to deliver notice to the Indemnitor within a reasonable time after the commencement of any such action, if materially prejudicial to its ability to defend such action, shall relieve the Indemnitor of any liability to the Indemnatee under this Article 12 only to the extent arising from the tardiness or absence of such notice, but the omission so to deliver notice to the Indemnitor will not relieve it of any liability that it may have to any Indemnatee otherwise than under this Article 12. The Indemnatee shall cooperate fully with the Indemnitor and its legal representatives in the investigation of any action, claim or liability covered by indemnification under this Article 12, at the expense of the Indemnitor.

12.9 Insurance. Abbott shall at its expense maintain, through self-insurance or otherwise, product liability insurance with respect to the development, manufacture, sale and use of Products and Program Compounds in such amounts and on such terms as Abbott customarily maintains with respect to its other similar products. Abbott shall maintain such insurance for so long as it continues to develop, manufacture or sell any Products or Program Compounds, and thereafter for so long as Abbott customarily currently maintains such insurance.

12.10 Acknowledgment. Abbott and John Hancock acknowledge that Abbott has not delivered or disclosed the contents of any of the In-License Agreements to John Hancock.

### ARTICLE 13 FORCE MAJEURE

Neither party shall be held liable or responsible to the other party nor be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including but not limited to fire, floods, embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, acts of God or acts, omission or delays in acting by any governmental authority; provided that such affected party shall provide the other party with prompt notice of the circumstances surrounding such a material failure or delay, after which the parties will amend this Agreement upon terms and conditions that are mutually agreeable to equitably account to the party that does not so fail or delay.

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#### ARTICLE 14 ASSIGNMENT

Except as expressly provided hereunder, this Agreement may not be assigned or otherwise transferred, nor may any right or obligations hereunder be assigned or transferred by either party without the consent of the other party; and, in addition, both parties acknowledge and agree that the obligations of Abbott hereunder are personal to Abbott and that Abbott is uniquely qualified to perform them; provided, however, that either party shall be obligated to assign this Agreement and its rights and obligations hereunder in connection with the transfer or sale of all or substantially all of its business, or in the event of its merger or consolidation or change in control or similar transaction and in such event such party shall cause its successor or transferee in such transaction to assume all of the obligations of such party. Any permitted assignee shall assume all obligations of its assignor under this Agreement. Notwithstanding the foregoing, John Hancock shall have the right to assign its rights (but not its obligation to make payments under Section 3.1) in whole or in part (provided that, any assignment in part shall mean an assignment of a pro rata share of the entirety of John Hancock's rights hereunder) without Abbott's consent (and following any such assignment all references to John Hancock herein shall include any such assignee), provided that: (i) each assignee of such rights must be a bank, insurance company or other institutional investor; (ii) there shall be no greater than five (5) assignees, (iii) if any such assignee is located outside the United States John Hancock shall notify Abbott at least sixty (60) days in advance, (iv) if any claim arises with respect to Abbott's failure to make payments, then during the term of the Research Program (but in any event not longer than four years from the date hereof), any such claim must be brought by John Hancock, and not an assignee. In soliciting potential assignees for such right to payments, John Hancock shall not disclose any Confidential Information hereunder to more than ten (10) potential assignees. Any potential assignee to whom John Hancock discloses Confidential Information must have executed a confidentiality agreement no less stringent than Article 10 hereof. Furthermore, if John Hancock plans to exercise its right of assignment hereunder, John Hancock shall first notify Abbott of such plans in writing. Abbott shall have the first right to negotiate the purchase of any such assignment rights. If within fifteen (15) days after receipt of such notice the parties have not agreed upon the principal terms of such arrangement or if within forty-five (45) days after receipt of such notice the parties have not executed a final written agreement reflecting such arrangement, then John Hancock shall have no further obligations to Abbott with respect to such first right of negotiation.

#### ARTICLE 15 SEVERABILITY

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Each party hereby agrees that it does not intend its execution and delivery hereof or its performance hereunder to violate any public policy, statutory or common laws, rules, regulations, treaty or decision of any government agency or executive body thereof of any country or community or association of countries. If and to the extent any term or provision of this Agreement is held to be invalid, illegal or unenforceable by a court or other governmental

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authority of competent jurisdiction, such invalidity, illegality or unenforceability shall not affect any other term or provision of this Agreement, which shall remain in full force and effect. The holding of a term or provision to be invalid, illegal or unenforceable in a jurisdiction shall not have any effect on the application of the term or provision in any other jurisdiction.

ARTICLE 16  
MISCELLANEOUS

16.1 Notices. Any consent, notice or report required or permitted to be given or made under this Agreement by one of the parties hereto to the other shall be in writing, delivered personally or by facsimile (and promptly confirmed by personal delivery, U.S. first class mail or courier), U.S. first class mail or courier, postage prepared (where applicable), addressed to such other party at its address indicated below, or to such other address as the addressee shall have last furnished in writing to the addressor and (except as otherwise provided in this Agreement) shall be effective upon receipt by the addressee.

If to John Hancock: John Hancock Life Insurance Company  
200 Clarendon Street, T-57  
Boston, MA 02117  
Attention: Bond & Corporate Finance Group  
Telephone: 617-572-9624  
Fax: 617-572-1628

copy to: John Hancock Life Insurance Company  
200 Clarendon Street, T-50  
Boston, MA 02117  
Attention: Investment Law Division  
Telephone: 617-572-9205  
Fax: 617-572-9268

and, if it relates to making or not making a royalty payment or Milestone Payment hereunder,

copy to: John Hancock Life Insurance Company  
200 Clarendon Street  
Boston, MA 02117  
Attention: Manager, Investment Accounting Division, B-3  
Fax: 617-572-0628

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If to Abbott: Abbott Laboratories  
Dept. 309, Bldg. AP30  
200 Abbott Park Road  
Abbott Park, IL 60064-3537  
Attention: President, Pharmaceutical Products Division  
Telephone: 847-938-6863  
Fax: 847-938-5383

copy to: General Counsel  
Abbott Laboratories  
Dept. 364, Bldg. AP6D  
100 Abbott Park Road  
Abbott Park, IL 60064-6020  
Telephone: 847-937-8905  
Fax: 847-938-6277

16.2 Applicable Law. The Agreement shall be governed by and construed in accordance with the internal laws of the State of Illinois. With respect to any action hereunder, Abbott, to the extent that it may lawfully do so, hereby consents to service of process, and to be sued, in the Commonwealth of Massachusetts and consents to the exclusive jurisdiction of the courts of the Commonwealth of Massachusetts and the United States District Court for the District of Massachusetts, as well as to the jurisdiction of all courts to which an appeal may be taken from such courts, for the purpose of any suit, action or other proceeding arising out of any of its obligations hereunder or thereunder or with respect to the transactions contemplated hereby or thereby, and expressly waives any and all objections it may have as to venue in any such courts. Abbott further agrees that a summons and complaint commencing an action or proceeding in any of such courts shall be properly served and shall confer personal jurisdiction if served personally or by certified mail to it at its address for notices as provided in this Agreement or as otherwise provided under the laws of the Commonwealth of Massachusetts. THE PARTIES EACH IRREVOCABLY WAIVE ALL RIGHT TO A TRIAL BY JURY IN ANY SUIT, ACTION OR OTHER PROCEEDING INSTITUTED BY OR AGAINST IT IN RESPECT OF ITS OBLIGATIONS HEREUNDER OR THEREUNDER OR THE TRANSACTIONS CONTEMPLATED HEREBY OR THEREBY.

16.3 Entire Agreement. This Agreement contains the entire understanding of the parties with respect to the subject matter hereof. All express or implied agreements and understandings, either oral or written, with respect to the subject matter hereof heretofore made are expressly merged in and made a part of this Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.

16.4 Headings. The captions to the several Articles and Sections hereof are not a part of this Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

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**JH 008113**

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16.5 Independent Contractors. It is expressly agreed that John Hancock and Abbott shall be independent contractors and that the relationship between the two parties shall not constitute a partnership, joint venture or agency. Neither John Hancock nor Abbott shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior written consent of the other party to do so.

16.6 Performance By Affiliates, Licensees and Subcontractors. The parties recognize that Abbott may carry out certain obligations under this Agreement through performance by its Affiliates, Licensees and Subcontractors (but in no event shall that relieve Abbott of any of its obligations hereunder). Abbott guarantees that the activities of its Affiliates, Licensees and Subcontractors under this Agreement shall comply with this Agreement.

16.7 Dispute Resolution. The parties shall attempt to amicably resolve disputes arising between them regarding the validity, construction, enforceability or performance of the terms of this Agreement, and any differences or disputes in the interpretation of the rights, obligations, liabilities and/or remedies hereunder, which have been identified in a written notice from one party to the other, by good faith settlement discussions between the President of Abbott's Pharmaceutical Products Division and a Managing Director of John Hancock or his designee. The parties agree that, prior to filing any lawsuit regarding any dispute that arises in connection with this Agreement (with the exception of any action demanding a preliminary injunction), such representatives shall meet and attempt to amicably resolve such dispute within thirty (30) days after the receipt of such written notice.

16.8 Waiver. The waiver by either party hereto of any right hereunder or the failure to perform or of a breach by the other party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.

16.9 Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

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IN WITNESS WHEREOF, the parties have executed this Agreement as of the date first set forth above.

JOHN HANCOCK LIFE  
INSURANCE COMPANY

ABBOTT LABORATORIES

By: Stephen J. Blewitt  
Name: Stephen J. Blewitt

By: Jeffrey M. Leiden  
Name: Jeffrey M. Leiden, Ph.D., M.D.

Title: Managing Director

Title: Executive Vice President, Pharmaceuticals  
and Chief Scientific Officer

Date: March 13, 2001

Date: March 13, 2001

JOHN HANCOCK VARIABLE  
LIFE INSURANCE COMPANY

By: Stephen J. Blewitt  
Name: Stephen J. Blewitt

Title: Authorized Signatory

Date: March 13, 2001

INVESTORS PARTNER LIFE INSURANCE  
COMPANY

By: Stephen J. Blewitt  
Name: Stephen J. Blewitt

Title: Authorized Signatory

Date: March 13, 2001

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EXHIBIT 1.6

FIRST ANNUAL RESEARCH PLAN

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**JH 008116**

Ketolide Oral & IV (ABT-773)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Antibacterial										
Indications	Adult Tablet: Community-acquired respiratory infections. I.V.: Step-down therapy in community-acquired hospitalized pneumonia.										
Description	<ul style="list-style-type: none"><li>- ABT-773 is a potent ketolide with strong activity against most macrolide resistant strains, while maintaining the broad spectrum coverage of clarithromycin.</li><li>- Product will be available as tablet and IV formulation.</li><li>- ABT-773 will address the major unmet medical needs of increasing resistance to current empiric agents, particularly S. pneumonia.</li><li>- Maintains clari's claim of "Spans the spectrum" (G+, G-, atypicals).</li><li>- Cover key G+ resistant strains (S. pneumonia, S. pyogenes).</li><li>- Tablet dosing is 150mg QD or 150mg BID dosing based on severity of indications.</li><li>- Tablet: 5 days for ABECB, pharyngitis, 10 days for AMS and CAP.</li><li>- Incidence of GI side effects equal to clari (assuming comparable drug levels to tablet).</li><li>- COGS target \$2,500/kg at launch for tablet.</li></ul>										
Current Time Line	Milestone		Tablet Date		IV Date		Spending		\$		
	Phase I	1Q1997	1Q2001		Project-to-Date-Spending (thru '00)		188.4				
	Phase IIb	3Q1999	N/A		2001 Current Projection (Plan)		91.5*				
	Phase III	4Q2000	4Q2001								
	NDA Filing	3Q2002	2Q2003								
	Launch	1Q2004	2Q2004								
	* See page 2 for detail.										
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total				
	74.1	91.5	69.0	45.0	32.0	22.0	333.6				

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JH 008117





Endothelin (ABT-627)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Oncology									
Indications	<ul style="list-style-type: none"><li>- Hormone Refractory Prostate Cancer</li><li>- Potential for use in early Prostate Cancer and other cancer types</li></ul>									
Description	<ul style="list-style-type: none"><li>- ABT-627 is Abbott's leading endothelin antagonist receptor</li><li>- ABT-627 is seeking an indication for the treatment of hormone refractory prostate cancer</li><li>- ABT-627 will probably be used with current therapies</li><li>- Well tolerated as chronic therapy</li><li>- Oral administration</li><li>- No major drug interactions with drugs commonly used in elderly population or hormonal therapy</li><li>- Demonstrated cost effectiveness at filing</li></ul>									
Current Time Line	Milestone	Date							Spending	\$
	Phase I	2Q1996							Project-to-Date-Spending (thru '00)	127.6
	Phase II	4Q1997							2001 Current Projection (Plan)	38.0*
	Phase III	4Q2000								
	NDA Filing	2Q2004								
	Launch	4Q2004								
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total			
PC*	13.0	38.0	40.0	33.0	20.0	10.0	154.0			
EPcA*	N/A	6.0	6.0	5.0	0.0	0.0	17.0			
FE*	N/A	5.0	3.0	0.0	0.0	0.0	8.0			

\* End of Phase II meeting with FDA just completed. Budget impact still in process plus discussion of other cancer indications ongoing. 2001 range \$35-40 depending on outcome of discussion.

\* See page 2 for detail.

\* End of Phase II meeting with FDA just completed. Budget impact still in process plus discussion of other cancer indications ongoing. 2001 range \$35-40 depending on outcome of discussion.

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CCM (ABT-594)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Neuroscience									
Indications	ABT-594 primary target indication is the treatment of neuropathic pain (NP).									
Description	<ul style="list-style-type: none"> <li>- ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator.</li> <li>- ABT-594 is effective in nociceptive pain and neuropathic pain.</li> <li>- ABT-594 is expected to have a better side effect profile than opioids, no tolerance, no abuse, and no DEA scheduling.</li> <li>- Pre clinical data show ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in treating moderate to severe pain in several well characterized animal models of pain.</li> <li>- ABT-594 has a unique mechanism of action which may enable use in combination with other analgesics as well as monotherapy.</li> <li>- Slow onset of action (approx. 1.5 - 3 hours) at low doses tested may suggest limited utility in acute pain types.</li> <li>- Favorable safety profile.</li> <li>- Oral formulation, BID dosing.</li> </ul>									
Current Time Line	Milestones	Date	Spending							\$\$
	IND Filing	4Q1998	Project-to-Date-Spending (thru '00)							97.3
	Phase I	3Q1997								35.0*
	Phase II	3Q1998	2001 Current Projection (Plan)							
	Phase III	4Q2001								
	NDA Filing	3Q2003	* See page 2 for detail.							
	Launch	3Q2004								
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total			
	14.4	35.0	45.0	32.0	15.0	12.0	153.4			

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Quinolone (ABT-492)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Anti-bacterial																			
Indications	<ul style="list-style-type: none"><li>- Community acquired respiratory, nosocomial pneumonia, complicated and uncomplicated urinary tract and skin/soft tissue infections.</li><li>- ABT-492 is a potent broad-spectrum quinolone with activity against Gram+, Gram-, and atypical pathogens, including most penicillin, macrolide, and quinolone resistant strains of S. pneumo.</li><li>- Commercial objective is "Trovan-like" activity with "Levaquin-like" safety.</li><li>- Preliminary in-vitro safety assays suggest good safety profile.</li><li>- Product will be available in tablet and injectable formulations.</li><li>- Targeting QD dosing for both formulations (not confirmed).</li><li>- Targeting 5-7 day dosing for most indications (not confirmed).</li><li>- COGS at \$1,500-3,200/kg at launch pending chemistry optimization.</li></ul>																			
Description																				
Current Time Line	<table><tr><th>Milestone</th><th>Date</th></tr><tr><td>Phase I</td><td>4Q2000</td></tr><tr><td>Phase II</td><td>3Q2001</td></tr><tr><td>Phase III</td><td>3Q2002</td></tr><tr><td>NDA Filing</td><td>4Q2004</td></tr><tr><td>Launch</td><td>4Q2005</td></tr></table>	Milestone	Date	Phase I	4Q2000	Phase II	3Q2001	Phase III	3Q2002	NDA Filing	4Q2004	Launch	4Q2005	<table><tr><th>Spending</th><th>\$</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>11.3</td></tr><tr><td>2001 Current Projection (Plan)</td><td>25.0*</td></tr></table> <p>* See page 2 for detail.</p>	Spending	\$	Project-to-Date-Spending (thru '00)	11.3	2001 Current Projection (Plan)	25.0*
Milestone	Date																			
Phase I	4Q2000																			
Phase II	3Q2001																			
Phase III	3Q2002																			
NDA Filing	4Q2004																			
Launch	4Q2005																			
Spending	\$																			
Project-to-Date-Spending (thru '00)	11.3																			
2001 Current Projection (Plan)	25.0*																			
Projected Spending by Year	<table><tr><th>2000</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>Total</th></tr><tr><td>6.8</td><td>25.0</td><td>75.0</td><td>100.0</td><td>52.0</td><td>11.0</td><td>269.8</td></tr></table>	2000	2001	2002	2003	2004	2005	Total	6.8	25.0	75.0	100.0	52.0	11.0	269.8					
2000	2001	2002	2003	2004	2005	Total														
6.8	25.0	75.0	100.0	52.0	11.0	269.8														

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Quinolone (ABT-492)  
2001 Plan Development Cost Summary

[illegible]

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TSP (ABT-510)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Oncology																											
Indications	Solid tumors such as lung, breast, ovary, bladder and pancreas.																											
Description	<ul style="list-style-type: none"><li>- Thrombospondin peptide</li><li>- Novel anti-angiogenesis agent</li><li>- Parenteral dosing</li><li>- ABT-510 is seeking an indication for the treatment of solid tumors</li><li>- Mechanism may prevent the growth of tumors and prevent the spread of metastases by preventing or inhibiting the growth of nutrient supplying blood vessels</li></ul>																											
Current Time Line	<table><tr><th>Milestone</th><th>Date</th></tr><tr><td>DDC</td><td>4Q1998</td></tr><tr><td>Phase I</td><td>2Q2000</td></tr><tr><td>Phase II</td><td>4Q2001</td></tr><tr><td>Phase III</td><td>1Q2003</td></tr><tr><td>NDA Filing</td><td>1Q2005</td></tr><tr><td>Launch</td><td>1Q2006</td></tr></table>	Milestone	Date	DDC	4Q1998	Phase I	2Q2000	Phase II	4Q2001	Phase III	1Q2003	NDA Filing	1Q2005	Launch	1Q2006	<table><tr><th>Spending</th><th>\$\$</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>45.6</td></tr><tr><td>2001 Current Projection (Plan)</td><td>9.0*</td></tr></table>				Spending	\$\$	Project-to-Date-Spending (thru '00)	45.6	2001 Current Projection (Plan)	9.0*	* See page 2 for detail.		
Milestone	Date																											
DDC	4Q1998																											
Phase I	2Q2000																											
Phase II	4Q2001																											
Phase III	1Q2003																											
NDA Filing	1Q2005																											
Launch	1Q2006																											
Spending	\$\$																											
Project-to-Date-Spending (thru '00)	45.6																											
2001 Current Projection (Plan)	9.0*																											
Projected Spending by Year	<table><tr><th>2000</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>Total</th></tr><tr><td>6.6</td><td>9.0</td><td>37.0</td><td>29.0</td><td>23.0</td><td>15.0</td><td>119.6</td></tr></table>	2000	2001	2002	2003	2004	2005	Total	6.6	9.0	37.0	29.0	23.0	15.0	119.6													
2000	2001	2002	2003	2004	2005	Total																						
6.6	9.0	37.0	29.0	23.0	15.0	119.6																						

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**TSP (ABT-510)**  
**2001 Plan Development Cost Summary**

Program Status	1998				1999				2000				2001				2002				2003				2004				2005			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																

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MMPI (ABT-518)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area		Oncology						
Indications		Solid tumors such as lung, ovarian, pancreas, breast, colorectal and bladder.						
Description		<ul style="list-style-type: none"><li>- Novel metalloproteinase inhibitor.</li><li>- Cytostatic mechanism.</li><li>- Oral dosing.</li><li>- May prevent the growth of metastatic lesions and/or inhibit primary tumor growth.</li><li>- Superior efficacy or side-effect profile to competitive agents.</li></ul>						
Current Time Line	Milestone	Date					Spending	
	DDC Phase I Phase II Phase III NDA Filing Launch	1Q2000 1Q2001 3Q2002 4Q2003 4Q2005 2Q2006	Project-to-Date-Spending (thru '00)  2001 Current Projection (Plan)  * See page 2 for detail.					40.0  7.0*
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total	
	5.0	7.0	31.0	35.0	26.0	20.0	124.0	

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MMPI (ABT-518)  
2001 Plan Development Cost Summary

Program Status	1999				2000				2001				2002				2003				2004				2005				2006			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																
NDA																																

Anti-Mitotic (ABT-751)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Oncology						
Indications	Solid tumors such as breast, lung, colorectal, and ovarian						
Description	<ul style="list-style-type: none"><li>- Novel oral cytotoxic agent that inhibits tumor growth by inhibiting the polymerization of tubulin, similar to the MOA of taxanes</li><li>- May be effective in patients resistant to other cytotoxic agents</li></ul>						
Current Time Line	Milestone	Date	Spending				\$ \$
	In-License	2Q2000					Project-to-Date-Spending (thru '00) 2001 Current Projection (PLAN)  * See page 2 for detail.
	Phase I	1Q/2001					
	Phase II	4Q/2001					
	Phase III	4Q/2002					
	NDA Filing	1Q/2005					
	Launch	1Q/2006					6.0
							10.0*
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
	6.0	10.0	27.0	35.0	25.0	12.0	115.0

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Anti-Mitotic (ABT-751)  
2001 Plan Development Cost Summary

2001 Plan Development Cost Summary

Program Status	1998				1999				2000				2001				2002				2003				2004							
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4								
Phase I																																
Phase II																																
Phase III																																
↑ In-license																																
Major Development Activities and Costs																																
Clinical Program	Total Patients												Enrolled as of 8/31/00				Start				End				2000 AGU Cost				2001 Plan Cost			
Multiple Dose in Cancer Patients #1	24												...				Jan-2001				Nov-2001				...				\$600			
Multiple Dose in Cancer Patients #2	24												...				Apr-2001				May-2002				...				\$466			
Safety and Efficacy #1-#6	180												...				Aug-2001				Oct-2002				...				\$1,092			
Other Studies / EVR																													...			
Venture Management																													\$2,762			
Data Management/Statistics																													<u>\$413</u>			
																													<u>\$5,333</u>			
Chemistry, Manufacturing, and Controls (CMC)																									2000 AGU				2001 Plan			
Formulation / Analytical																									...				\$2,300			
Drug Safety Support																									2000 AGU				2001 Plan			
Ongoing Drug Safety support.																									...				\$1,685			
Other Support Costs																									2000 AGU				2001 Plan			
Discovery																									...				\$26			
Medical Affairs																									...				...			
Regulatory Affairs / Research Quality Assurance																									...				\$301			
Other / In-Licensing Fees																									<u>\$6,000</u>				<u>\$355</u>			
Total Program																									<b>\$6,000</b>				<b>\$10,000</b>			

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FTI (ABT-xxx)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area		Oncology						
Indications		Solid tumors such as lung, breast, ovary, bladder and pancreas.						
Description		- Farnesyltransferase Inhibitor.						
		- Mechanism of action is unknown, but thought to inhibit farnesylated proteins which are integral for malignant tumor growth.						
Current Time Line	Milestones	Date					Spending	\$\$
	DDC Phase I Phase II Phase III NDA Filing Launch	1Q/2001 4Q/2001 2Q/2003 3Q/2004 4Q/2006 4Q/2007					Project-to-Date-Spending (thru '00)  2001 Current Projection (Plan)  * See page 2 for detail.	35.0  6.0*
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total	
	N/A	6.0	15.0	30.0	30.0	18.0	99.0	

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Dopamine Receptor Agonist (ABT-xxx)  
Annual Development Plan  
Exhibit 1.6

Therapeutic Area	Other															
Indications	Male Erectile Dysfunction (MED)															
Description	<ul style="list-style-type: none"><li>- D4 Dopamine Receptor Agonist.</li><li>- Targets D4 receptors in the brain which offers the potential for efficacy in patients with MED that do not respond to Viagra.</li><li>- Additionally this approach offers opportunity for compounds with improved tolerability relative to other Dopamine agents that are clinically used for MED.</li></ul>															
	Current Time Line	<table><tr><th>Milestones</th><th>Date</th></tr><tr><td>DDC</td><td>4Q/2001</td></tr><tr><td>Phase I</td><td>2Q/2002</td></tr><tr><td>Phase II</td><td>4Q/2003</td></tr><tr><td>Phase III</td><td>1Q/2005</td></tr><tr><td>NDA Filing</td><td>1Q/2007</td></tr><tr><td>Launch</td><td>4Q/2007</td></tr></table>	Milestones	Date	DDC	4Q/2001	Phase I	2Q/2002	Phase II	4Q/2003	Phase III	1Q/2005	NDA Filing	1Q/2007	Launch	4Q/2007
Milestones	Date															
DDC	4Q/2001															
Phase I	2Q/2002															
Phase II	4Q/2003															
Phase III	1Q/2005															
NDA Filing	1Q/2007															
Launch	4Q/2007															
Projected Spending by Year	<table><tr><th colspan="2">Spending</th><th>\$ \$</th></tr><tr><td colspan="2">Project-to-Date-Spending (thru '00)</td><td>35.0</td></tr><tr><td colspan="2">2001 Current Projection (Plan)</td><td>6.0*</td></tr></table>		Spending		\$ \$	Project-to-Date-Spending (thru '00)		35.0	2001 Current Projection (Plan)		6.0*					
	Spending		\$ \$													
Project-to-Date-Spending (thru '00)		35.0														
2001 Current Projection (Plan)		6.0*														
	* See page 2 for detail.															
	<table><tr><th>2000</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>Total</th></tr><tr><td>N/A</td><td>6.0</td><td>15.0</td><td>30.0</td><td>30.0</td><td>18.0</td><td>99.0</td></tr></table>		2000	2001	2002	2003	2004	2005	Total	N/A	6.0	15.0	30.0	30.0	18.0	99.0
2000	2001	2002	2003	2004	2005	Total										
N/A	6.0	15.0	30.0	30.0	18.0	99.0										

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Pharmaceutical Products Division  
Sample Direct/Indirect Project Funding Distribution  
2001 Plan (\$000)

	ABT - 773 (Late Stage - Phase III)			MMPI (Early Stage)		
	Direct	Indirect	Total	Direct	Indirect	Total
PPD Investigational Drug	0.3	0.0	0.4	-	-	-
Venture Management	4.8	1.6	6.5	0.8	0.2	0.9
Discovery	2.2	0.2	2.4	1.1	0.3	1.3
Drug Safety	1.6	0.2	1.7	1.8	0.3	2.1
PARC	4.8	0.4	5.3	0.8	0.2	1.0
Phase I Center	2.0	0.1	2.1	0.1	0.0	0.1
Development Operations	4.2	0.5	4.6	0.1	0.0	0.1
Regulatory Affairs	0.2	0.0	0.3	0.0	0.0	0.0
Medical Affairs	0.8	0.1	0.9	0.0	0.0	0.0
Administration	1.6	-	1.6	0.1	-	0.1
AI Manpower	0.7	-	0.7	-	-	-
Bulk Drug / Process	15.0	-	15.0	-	-	-
Clinical Grants	43.1	-	43.1	1.3	-	1.3
<b>Total</b>	<b>81.4</b>	<b>3.2</b>	<b>84.6</b>	<b>6.2</b>	<b>0.9</b>	<b>7.1</b>
<b>% Split</b>	<b>96.2%</b>	<b>3.8%</b>	<b>100.0%</b>	<b>86.6%</b>	<b>13.4%</b>	<b>100.0%</b>

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**Pharmaceutical Products Division**  
**Sample Direct/Indirect Rate & Headcount Distribution**  
**2001 Plan**

<u>Rate:</u>	<u>Data Management</u>	<u>Toxicology/Pathology</u>
<b>Direct</b>		
Payroll (Both PMP and Supv/Mgr)	6,577	5,277
Office Supplies	53	51
T & E	26	84
Sem/Edu	21	73
Supplies	41	440
Consultant	291	67
Printing	73	4
Clinical Tracking Costs	4,075	...
Depreciation	1,031	258
UNIX Based Support	3,453	921
Utilities	62	...
Floorspace	579	1,479
Housekeeping	23	...
Other	112	389
<b>Sub-Total Direct</b>	<b>16,416</b>	<b>9,042</b>
<b>Indirect</b>		
Patents & Trademarks	285	388
Corporate Indirect	697	949
PPD Indirect (Mgmt.)	337	458
Department Overhead	396	584
Other	46	62
<b>Sub-Total Indirect</b>	<b>1,761</b>	<b>2,441</b>
<b>Total</b>	<b>18,177</b>	<b>11,483</b>
<b>% Direct</b>	<b>90%</b>	<b>79%</b>
<b>% Indirect</b>	<b>10%</b>	<b>21%</b>
<u><b>Headcount:</b></u>		
Direct Headcount	123 88%	53 88%
Indirect Headcount	17 12%	7 12%
<b>Total Headcount</b>	<b>140</b>	<b>60</b>
<b>Rate</b>	<b>92.06</b>	<b>135.42</b>
<b>Hours</b>	<b>1,600</b>	<b>1,600</b>
<b>Annual Rate</b>	<b>147,296</b>	<b>216,672</b>

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EXHIBIT 1.17

EISAI TERRITORY

1. Bhutan
2. Brunei
3. Cambodia
4. People's Republic of China
5. Republic of China (Taiwan)
6. India
7. Indonesia
8. Japan
9. Democratic People's Republic of Korea (North Korea)
10. Republic of Korea
11. Laos
12. Macao
13. Malaysia
14. Mongolia
15. Myanmar
16. Nepal
17. Pakistan
18. Papua New Guinea
19. Philippines
20. Singapore
21. Sri Lanka
22. Thailand
23. Vietnam
24. Italy, co-exclusive rights with Abbott, unless Abbott exercises its rights under the terms of the Eisai Agreement to take an exclusive right to Italy.

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## EXHIBIT 1.40

PROGRAM COMPOUNDS

<u>In-License Agreement</u>	<u>Program Compound</u>	<u>Development Phase</u>
	ABT-627 (Endothelin antagonist)	phase III
Taisho	ABT-773 (Ketolide antibiotic)	phase III
	ABT-594 (Cholinergic channel modulator)	late phase II
Wakunaga	ABT-492 (Quinolone antibiotic)	phase I
Eisai	ABT-751 (Antimitotic)	phase I
	ABT-510 (Thrombospondin peptide)	phase I
<u>Preclinical Programs:</u>		
FTI Program		late preclinical
ED Program		late preclinical
MMPI Program	ABT-518 (Matrix metalloproteinase inhibitor)	phase I

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EXHIBIT 1.43

EXAMPLE OF PROGRAM RELATED COSTS FOR ONE PROGRAM COMPOUND

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2001 KEY RATES									
	2000		2001		% Change				
	Rate	Hours	Rate	Hours	Rate	Hours	Hourly Rate	Total Hours	Annual Rate
<u>DRUG SAFETY</u>									
Toxicology/Pathology - PMP/TMP	121.52	1,680	204,154	1,600	135.42	1,600	11.4%	-4.8%	6.1%
Metabolism/Microscopy - PMP/TMP	144.75	1,600	231,600	1,650	141.64	1,650	-2.1%	3.1%	0.9%
Comparative Medicine - PMP/TMP	115.60	1,768	204,381	1,850	116.88	1,850	1.1%	4.6%	5.8%
Strategic & Exploratory - PMP/TMP	121.52	1,680	204,154	1,600	173.56	1,600	42.8%	-4.8%	36.0%
<u>PHASE I CENTER</u>									
Pharmacokinetics 4PK -PMP/TMP	144.75	1,600	231,600	1,600	135.00	1,600	-6.7%	...	-6.7%
Clin. Res. MDs 42P - PMP	...	...	...	1,500	180.35	1,500	...	...	...
Clin Res. Spec. 420-PMP/TMP	113.59	1,700	193,103	1,700	123.75	1,700	8.9%	...	8.9%
<u>PARD</u>									
Prod Dev - PMP, TMP	108.54	1,800	195,372	1,800	116.71	1,800	7.5%	...	7.5%
IDS - PMP, TMP	160.80	1,600	257,280	1,600	162.11	1,600	0.8%	...	0.8%
<u>DEV OPERATIONS</u>									
Data Mgmt D433 - TMP/PMP	90.04	1,600	144,064	1,600	92.06	1,600	2.2%	...	2.2%
Stats - PMP/TMP	97.75	1,800	175,950	1,800	99.10	1,800	1.4%	...	1.4%
<u>RA/QA</u>									
RA/QA - PMP & TMP	125.50	1,600	200,800	1,600	134.49	1,600	7.2%	...	7.2%
<u>DISCOVERY</u>									
	137.65	1,800	247,770	1,800	142.91	1,800	3.8%	...	3.8%

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EXHIBIT 9.2

PAYMENT INSTRUCTIONS

Fleet Boston  
ABA No. 011000390  
Boston, Massachusetts 02110  
Account of: John Hancock Life Insurance Co. Private Placement Collection Acct.  
Account Number: 541-55417  
On Order of: Abbott Laboratories -- Research Funding Agreement dated as of March 13, 2001

E-3233160

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## Exhibit 12.2(d)

## Further Information Regarding Program Compounds

COMPOUND	CHEMICAL NAME	CURRENT STAGE OF DEVELOPMENT
ABT-627 Endothelin antagonist	(2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-3-pyrrolidinecarboxylic acid	Phase III
ABT-773 Ketolide antibiotic	(3aS,4R,7R,9R,10R,11S,13R,15R,15aR)-4-ethyl-3a,7,9,11,13,15-hexamethyl-2,6,8,14-tetraoxo-11-[[[(2E)-3-(3-quinolinyl)-2-propenyl]oxy]tetradecahydro-2H-oxacyclotetradecino[4,3-d][1,3]oxazol-10-yl 3,4,6-trideoxy-3-(dimethylamino)-D-xylo-hexopyranoside	Phase III
ABT-594 Cholinergic channel modulator	(2R)-azetidylmethyl 6-chloro-3-pyridinyl ether hydrochloride	Phase II
ABT-492 Quinoline Antibiotic	potassium 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-7-(3-hydroxy-1-azetidynyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate	Phase I
ABT-518 Matrix metalloproteinase inhibitor	(1S)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[(4-{4-(trifluoromethoxy)phenoxy}phenyl)sulfonyl]ethyl(hydroxy)formamide	Phase I
ABT-751 Antimitotic	N-[2-(4-hydroxyanilino)-3-pyridinyl]-4-methoxybenzenesulfonamide	Phase I
Farnesyltransferase inhibitor	N.A.	Pre-Clinical Program
Dopamine Receptor Agonist for Erectile Dysfunction	N.A.	Pre-Clinical Program

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# PART 4

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## EXHIBIT 12.2(e)

## Certain Patent Information

ABT-627

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	08/04/1995	711832	<i>Issued</i>	08/04/2015
Brazil	02/12/1997		<i>Pending</i>	
Canada	08/04/1995		<i>Pending</i>	
EP*	08/04/1995		<i>Pending</i>	
Hong Kong	07/15/1998		<i>Pending</i>	
Israel	08/10/1995		<i>Pending</i>	
Japan	08/04/1995		<i>Pending</i>	
Korea	08/04/1995		<i>Pending</i>	
Mexico	08/04/1995		<i>Pending</i>	
Philippines	08/17/1995		<i>Pending</i>	
USA	05/30/1995	5,767,144	<i>Issued</i>	06/16/2015

\*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

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## Exhibit 12.2(e) (Cont'd)

ABT-773  
(Subject to Taisho Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	09/03/1997		Pending	
Australia	09/02/1997		Pending	
Brazil	05/13/1997		Pending	
Brazil	09/02/1997		Pending	
Bulgaria	09/02/1997		Pending	
Belarus	09/02/1997		Pending	
China	09/02/1997		Pending	
Chile	09/04/1997		Pending	
Canada	09/02/1997		Pending	
Columbia	09/02/1997		Pending	
Czech Republic	09/02/1997		Pending	
EP*	09/02/1997		Pending	
Guatemala	08/29/1997		Pending	
Hong Kong	09/02/1997		Pending	
Croatia	09/03/1997		Pending	
Hungary	09/02/1997		Pending	
Indonesia	09/04/1997		Pending	
India	Pending-Black Box		Pending	
Israel	09/02/1997		Pending	
Japan	09/02/1997		Pending	
Korea	09/02/1997		Pending	
Mexico	09/02/1997		Pending	
Malaysia	08/26/1997		Pending	
Norway	09/02/1997		Pending	

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## Exhibit 12.2(e) (cont'd)

ABT-773 (cont'd)  
(Subject to Taisho Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
New Zealand	09/02/1997		Pending	
Philippines	09/02/1997		Pending	
Pakistan	10/13/1997	136010	Issued	10/13/2013
Poland	09/02/1997		Pending	
Romania	09/02/1997		Pending	
Russia	09/02/1997		Pending	
South Africa	08/20/1997	97/7474	Issued	08/20/2017
Singapore	09/02/1997		Pending	
Slovak Republic	09/02/1997		Pending	
Slovenia	09/02/1997	20023	Issued	09/02/2017
Saudi Arabia	02/10/1998		Pending	
Thailand	09/03/1997		Pending	
Turkey	09/02/1997	TR 01127 B	Issued	09/02/2017
Taiwan	09/05/1997		Pending	
UA	09/02/1997		Pending	
USA	07/03/1997	5,866,549	Issued	09/04/2016
Yugoslavia	09/02/1997		Pending	

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## EXHIBIT 12.2(e) (Cont'd)

ABT-594

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	10/08/1993	687017	Issued	10/18/2013
Brazil	04/30/1997		Pending	
Canada	10/08/1993		Pending	
EP*	10/08/1993		Pending	
Hong Kong	12/10/1998		Pending	
Israel	10/04/1993	107184	Issued	10/04/2013
Japan	10/08/1993	3098035	Issued	10/08/2013
Korea	10/08/1993		Pending	
Mexico	10/08/1993		Pending	
Philippines	10/07/1993		Pending	
USA	06/07/1995	5,948,793	Issued	09/07/2016

\*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

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## EXHIBIT 12.2(e) (Cont'd)

ABT-492

(Subject to Wakunaga Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	09/24/1999		Pending	
Brazil	11/29/1999		Pending	
Canada	12/06/1999		Pending	
China	10/22/1999	1258674A	Issued	
Hong Kong				
EP*	12/08/1999	0992501	Issued	
Hungary	11/23/1999	9904389	Issued	
Republic of Korea	08/29/2000			
Mexico	10/14/1999		Pending	
Russian Federation	05/26/2000		Pending	
USA	06/10/1999		Pending	
Japan	10/06/1999	2000-136191	Issued	

\*Europe: Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, Great Britain, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Sweden

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## EXHIBIT 12.2(e) (Cont'd)

ABT-510

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	05/21/1999		Pending	
Australia	05/21/1999		Filing in Process	
Brazil	05/21/1999		Filing in Process	
Bulgaria	05/21/1999		Filing in Process	
China	05/21/1999		Filing in Process	
Chile	05/20/1999		Pending	
Canada	05/21/1999		Filing in Process	
Columbia	05/21/1999		Pending	
Czech Republic	05/21/1999		Filing in Process	
EP*	05/21/1999		Filing in Process	
Hong Kong	05/21/1999		Filing in Process	
Hungary	05/21/1999		Pending	
India	05/21/1999		Filing in Process	
Israel	05/21/1999		Filing in Process	
Japan	05/21/1999		Filing in Process	
Korea	05/21/1999		Filing in Process	
Mexico	05/21/1999		Filing in Process	
Norway	05/21/1999		Filing in Process	
New Zealand	05/21/1999		Filing in Process	
Philippines	05/21/1999		Pending	
Poland	05/21/1999		Filing in Process	
South Africa	05/21/1999		Filing in Process	
Slovak Republic	05/21/1999		Filing in Process	
Saudi Arabia	05/21/1999		Pending	
Turkey	05/21/1999		Filing in Process	
Taiwan	05/21/1999		Pending	
USA	05/21/1999		Pending	

\*Europe: Austria, Belgium, Great Britain, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland

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## EXHIBIT 12.2(e) (Cont'd)

ABT-518

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	07/30/1998		Pending	
Australia	07/27/1998		Pending	
Brazil	07/27/1998		Pending	
Bulgaria	07/27/1998		Pending	
China	07/27/1998		Pending	
Chile	07/17/1998		Pending	
Canada	07/27/1998		Pending	
Columbia	07/29/1998		Pending	
Czech Republic	07/27/1998		Pending	
EP*	07/27/1998		Pending	
Hungary	07/27/1998		Pending	
Israel	07/27/1998		Pending	
Japan	07/27/1998		Pending	
Korea	07/27/1998		Pending	
Mexico	07/27/1998		Pending	
Norway	07/27/1998		Pending	
New Zealand	07/27/1998		Pending	
Philippines	07/27/1998		Pending	
Poland	07/27/1998		Pending	
South Africa	07/30/1998	98/6828	Issued	07/30/2018
Slovak Republic	07/27/1998		Pending	
Saudi Arabia	12/15/1998		Pending	
Turkey	07/27/1998		Pending	
Taiwan	07/31/1998		Pending	
USA	08/05/1998		Pending	

\*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

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EXHIBIT 12.2(e) (Cont'd)

ABT-751  
(Subject to Eisai Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
USA	08/08/1991	5,250,549 5,292,758	Issued	08/08/2011 08/08/2011
Germany	08/07/1991	EP 472,053	Issued	08/07/2011
United Kingdom	08/07/1991	EP 472,053	Issued	08/07/2011
France	08/07/1991	EP 472,053	Issued	08/07/2011

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EXHIBIT 12.2(f)

COMMUNICATIONS

With respect to ABT-594, Abbott has received the following communications:

- ♦ Correspondence from Sibia Neurosciences, 505 Coast Blvd. South, Suite 300, La Jolla, CA 92037 (Sibia was acquired by Merck & Co., Inc. in August, 1999) including, most recently, a letter dated March 13, 1998.
- ♦ Correspondence from ICT Pharmaceuticals c/o Stadheim and Gear, Ltd., 400 North Michigan Ave., Chicago, IL 60611 including, most recently, a letter dated September 14, 2000.

The Sibia and ICT correspondence each refer to their patents on research tools.

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EXHIBIT 12.2(i)

Compound Reports

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**JH 008152**

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ABT – 773

**Descriptive Memorandum**

*February 2001*

Abbott Laboratories

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**JH 008153**

## ABT-773

### Opportunity Overview

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase II/III trials. Phase III clinical trials began in Q4, 2000. ABT-773 has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

### The US Market

The overall antibiotic market in the U.S. reached \$8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of the quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR <sub>95-99</sub>	TRXs (MM)	Share	CAGR <sub>95-99</sub>
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Ceftin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Cefzil	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$408.3	7.1%	-14.7%	30.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.0%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Augmentin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$590.5	10.3%	-1.1%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	\$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

### *U.S. Market Projections*

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

### *The Ex-U.S. Market*

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rxs) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rxs (29 million Rxs) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

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**Scientific Rationale for ABT-773**

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant Gram + organisms, particularly macrolide-resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

**Clinical Studies**

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	8% (6/79)

Clinical and Bacterial Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarrhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)		1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever		2% (2/85)	1% (2/169)

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The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Doses of 150mg QD, 300mg QD, and 600mg QD were tested. Of the enrolled subjects, 342 were clinically evaluable, and 169 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S.pneumoniae</i>	83%	(10/12)	90%	(9/10)	100%	(13/13)	91%	(32/35)
<i>M.catarrhalis</i>	80%	(8/10)	92%	(12/13)	91%	(10/11)	88%	(30/34)
<i>H. influenzae</i>	94%	(17/16)	89%	(17/19)	83%	(19/23)	88%	(53/60)
<b>Clinical Response</b>								
Cure	87%	(98/113)	90%	(105/117)	90%	(101/112)		
Failure	13%	(15/113)	10%	(12/117)	10%	(11/112)		
<b>Clinical &amp; Bacteriological Response</b>								
Cure	84%	(42/50)	88%	(49/56)	94%	(59/63)		
Failure	16%	(8/50)	12%	(7/56)	6%	(4/63)		
<b>Adverse Events</b>								
Taste Perversion	5%	(4/84)	19%	(25/129)	29%	(37/129)	17%	(66/384)
Diarrhea	13%	(16/126)	12%	(15/129)	21%	(27/129)	15%	(58/384)
Nausea	7%	(9/126)	13%	(17/129)	30%	(38/129)	17%	(64/384)
Vomiting	2%	(3/126)	3%	(4/1229)	11%	(14/129)	5%	(21/384)
Nausea & Vomiting	0	(0/126)	<1%	(1/129)	4%	(5/129)	2%	(6/384)
Abdominal Pain	4%	(5/126)	4%	(5/129)	4%	(5/129)	4%	(15/384)

The safety and efficacy of ABT-773 in Acute Bacterial Sinusitis (ABS) were studied in a multi-center Phase IIb clinical trial conducted from October 1999 to March 2000. Dosing regimens of 150mg QD, 300mg QD, and 600mg QD were tested. Of the 292 enrolled subjects, 246 were clinically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		AB T-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S.pneumonia</i>	3/3		8/8		9/12		20/23	
<i>M. catarrhalis</i>	8/9		3/4		4/4		15/17	
<i>H. influenzae</i>	3/5		7/7		5/7		15/19	
<i>S.aureus</i>	1/1		1/1		3/4		5/6	
<b>Clinical Response</b>								
Cure	89%	(70/79)	83%	(70/84)	71%	(59/83)		
Failure	11%	(9/79)	17%	(14/84)	29%	(24/83)		
<b>Adverse Events</b>								
Taste Perversion	1%	16/97)	14%	(14/98)	27%	(26/97)	14%	(41/292)
Diarrhea	6%	(6/97)	6%	(6/98)	17%	(16/97)	10%	(28/292)
Nausea	3%	(3/97)	12%	(12/98)	26%	(25/97)	14%	(40/292)
Vomiting	1%	(1/97)	6%	(6/98)	17%	(16/97)	8%	(23/292)

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The safety and efficacy of ABT-773 in community-acquired pneumonia (CAP) were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Dosing regimens of 300mg QD and 600mg QD were tested. Of the 187 enrolled subjects, 1248 were clinically evaluable, and 15 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)	91%	(20/22)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)	67%	(8/12)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)	81%	(22/27)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)	93%	(27/29)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)	86%	(38/144)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)	100%	(5/5)
<b>Clinical Response</b>						
Cure	92%	(72/78)	80%	(56/70)		
Failure	8%	(6/78)	20%	(14/70)		
<b>Clinical &amp; Bacterial Response</b>						
Cure	92%	(54/59)	82%	(47/57)		
Failure	8%	(5/59)	18%	(10/57)		
<b>Adverse Events</b>						
Taste Perversion	17%	(16/95)	26%	(24/92)	21%	(40/187)
Diarrhea	14%	(13/95)	19%	(17/92)	16%	(30/187)
Nausea	12%	(11/95)	22%	(20/92)	17%	(31/187)
V omitting	10%	(9/95)	15%	(14/92)	12%	(23/187)

- Appendix 1

#### Key Emerging Competitors

Generic	Brand	Company	Class	Status
moxifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
gatifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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ABT – 627

**Descriptive Memorandum**

*February 2001*

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## ABT-627

### *Opportunity Overview*

ABT-627 is an orally bioavailable endothelin antagonist with a high selectivity for the Eta receptor. The endothelins (ET-1, ET-2, ET-3) are a family of 21 amino acid peptides first identified in 1988. Endothelin is a potent, long acting vasoconstrictor produced by vascular endothelial cells. The known biological effect of ET-1 are believed to be mediated principally through the Eta receptor. These include potent and uniquely sustained vasoconstriction of vascular smooth muscle, positive inotropy of myocardium, and the stimulation of cell proliferation or the hypertrophy in vascular smooth muscle cells, cardiac myocytes, and fibroblasts.

In vitro studies in cultured cells have established that ABT-627 selectively binds to the Eta receptor, and that ABT-627 is a potent inhibitor of ET-1 binding to the Eta receptor.

Studies in cultured human prostate cancer cells and other cultured cells have shown that ABT-627 acts as a functional antagonist of ET-1, and these effects have been confirmed in vivo by assessing the effect of ABT-627 on the ET-1 induced pressor response in rats. Further animal studies have suggested that oral ABT-627 may be effective in the treatment of congestive heart failure, pulmonary hypertension, hypertension, arterial restenosis, and myocardial infarction.

In addition to literature and animal models supporting the role of endothelin antagonists in cardiovascular indications, data exists supporting the role of the ET-1 cytokine as a pathogenic mediator in cancer.

The current role of endothelin in the manifestations of metastatic prostate cancer (PCA) and other tumors have yet to be fully defined. However, Abbott scientists and thought leaders have made multiple observations about endothelin biology which suggest that endothelin may play a role in the biology and pathophysiology of metastatic prostate disease and other metastatic disease such as ovarian, cervical and renal tumors

ABT-627 has successfully completed Phase II trials for PCA, and the results demonstrate efficacy in hormone refractory PCA. The end of Phase II meeting with the FDA was held on October 4<sup>th</sup>. The data from Phase II was very favorably received and "best package" comments were made. Fast track designation and rolling NDA were granted. The FDA was conceptually in agreement with preliminary design of Phase III clinicals and clinical end points to measure. While not a dictate, a second Phase III trial will likely be conducted to insure the best opportunity for a successful outcome. The Phase III program is scheduled to commence before year-end. It is expected that filing on ABT 627 will occur in US and ex-US 1Q 2004. The compound is also in Phase I trials for other cancer types. Phase II studies in other cancer types will commence in 2Q01. Other indications outside of oncology are also being considered, to optimize the commercial potential of this asset.

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### *The US Market*

Prostate cancer is the most common cancer to strike nonsmoking men. The NCI estimates that there are over 1.7 million men living with prostate cancer in the U.S., and another 179,300 will be diagnosed in 1999. Nearly 80% of these cases are men over 60 years of age. It is estimated that the prevalence of prostate cancer is 380,000 in Western Europe and 45,000 in Japan. While the vast majority of these patients will be identified with potentially curable disease (25% in Stage I and 50% in Stage II) in the U.S., half of these patients will go undiagnosed until late stage disease in W. Europe and Japan. The skewed distribution of diagnosed cases ex-U.S. is largely due to less aggressive prostate cancer screening programs compared to the U.S.

Prostate cancer has seen few additions or innovations in treatment regimens in the past two decades. Treatments remain, in general, radical prostatectomy (RP) for localized disease, radiotherapy for locally advanced disease and hormone therapy for advanced disease. Patients receiving hormone therapy become refractory to this treatment after two to three years, although many will continue on hormone therapy. These hormone refractory prostate cancer (HRPCa) patients usually have a life expectancy of approximately 12 months, and no existing standard of care exists for treating these patients. No therapy has shown a significant impact on survival in these patients, although some chemotherapeutic regimens may offer promise.

There is a general trend toward using hormone therapy in earlier stage patients. In some centers, patients are receiving hormone therapy prior to surgery or radiation, in an attempt to improve outcomes in these definitive treatments. Some thought leaders suggest that this earlier utilization has contributed to the overall mortality improvements in PCA. Studies are ongoing looking at different uses for hormone therapy, including intermittent therapy, in an attempt to improve outcomes and mitigate the morbidity associated with hormonal therapy.

Hormone therapy remains the mainstay of prostate cancer treatment in earlier stages. Chemotherapy, however, has gained additional attention in hormone refractory disease as new combinations and regimens offer the potential for greater therapeutic benefit with fewer side-effects. This trend will take several years before clinical trials are completed and community based oncologists adopt these regimens, so the current cytotoxic market in PCA is small.

The total dollar growth of this market has slowed as the two market leaders, Lupron (leuprolide/TAP) and Zoladex (goserelin/Zeneca), have experienced increased price pressures from managed care and Medicare. About half the states are currently reimbursing these therapies at a least cost option (only paying for the cheapest alternative), putting downward price pressures on Lupron (\$6,500/yr) to match Zoladex's (\$4,500/yr) lower price point. Thus, US Lupron dollar sales declined between 1997 and 1998, despite an increase in patient volume.

Growth has also stagnated due to a lack of innovation in this hormone dominated category. There have been few therapeutic advances in the treatment of PCA in the last 5 years.

The only chemotherapy approved for use in HRPCa patients with pain is Novantrone (mitoxantrone/Immunex), but the marginal benefits this compound delivers is deeply undercut by its severe toxicities and a lifetime cap on dose. Novantrone and steroids significantly reduced the metastatic pain in 40% of patients, but it does not appear to provide a survival advantage. Novantrone is dosed by i.v. infusion every 21 days, at a cost of \$560 per treatment, or an annual cost of around \$8,000. Use of this agent is associated with significant side-effects, including myelosuppression, cardiac toxicity (which limits dosing) and nausea. It is this negative side-effect profile that inhibits the use of this agent in more patients. Only about 4% of U.S. HRPCa patients received Novantrone therapy in 1998. Novantrone has not been approved ex-US.

Only about 17% of HRPCa patients received any chemotherapy in 1998. The most common drugs included estramustine, paclitaxel and etoposide. These drugs continue to be some of the most studied compounds in HRPCa ongoing research and represent the greatest short-term promise in the cytotoxic treatment of this advanced disease state.

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**US Sales of Products to Treat Prostate Cancer**

Product	1997 Dollar Sales (MM)	1998 Dollar Sales (MM)	% chng '97-'98
Lupron (leuprolide/TAP)	\$650	\$667	2.6%
Zoladex (goserelin/Zeneca)	233	296	27.3
Casodex (bicalutamide/Zeneca)	58	68	17.24
Eulixen (flutamide/Schering)	74	67	-9.5
Novantrone (mitoxantrone/Immunex)	33	35	6.1
Nilandrone (nilutamide/Hoechst)	12	24	100
Emcyt (estramustine/Pharmacia/Upjohn)	8	14	75
Taxol (paclitaxel/BMS)	4	8	100
VePesid (etoposide/BMS)	5	4	-20
Others	27	31	14.8
Total	1,104	1,214	10%

Source: Tandem Research and Price Probe

*US Market Projections*

- Novantrone (mitoxantrone/Immunex) is currently the only product approved for the treatment of hormone refractory PCA with pain. It currently falls short on the market needs in terms of efficacy and side-effect profile.

Attribute	Novantrone Profile
Dosing	I.V. infusion cycles
Cost	Expensive, ~\$10,000/yr
Efficacy	Provides marginal improvements in quality of life
Reimbursed	Yes
Side-effects	Dose limiting toxicities
Promo Efforts	108 oncology reps
Targets	Oncologists

Several surveys indicate that there are over 100 compounds in preclinical and clinical development for prostate cancer and various solid tumors. The compounds listed in the appendix represent compounds that appear to offer the greatest promise and/or potential for competition for ABT-627. However, since the most likely use of ABT-627 will be in combination with best therapy, it is difficult to define the extent of competitive threat that any of these compounds represent. In general, other cytostatic agents probably offer the greatest threat as a replacement for ABT-627. However, even other cytostatic agents may be combined to maximize the activity of the various mechanisms.

To date, PPD is aware of only one other endothelin receptor antagonist in development for cancer, from Yamanouchi, which began Phase I studies in the Fall of 1999. ABT-627 is still poised to be the first endothelin receptor antagonist to reach the market for oncology.

*Scientific Rationale for ABT-627*

There are relatively low hurdles for entry for a product to treat hormone refractory prostate cancer, as no truly effective agents presently exists. Quality of life is paramount in this population, followed by improvements in disease progression and survival. Quality of life parameters could include an impact on pain/or delay in pain onset or other performance type measures of daily activities. As all hormone therapy ultimately fails, a product that delays disease progression is needed.

Unmet Need	Pipeline Impact
Improvements in QOL	<ul style="list-style-type: none"> <li>ABT-627's profile goal is to provide improvements to a patient's QOL or blunt a decrease in QOL</li> <li>Cytotoxic agents rarely have significant positive impacts on QOL</li> <li>Other cytostatic agents may offer this benefit</li> </ul>
Improvements in survival	<ul style="list-style-type: none"> <li>It is unlikely that improvements in survival will be seen in our current trials</li> <li>Cytotoxic agents may offer a survival advantage, perhaps in combination with ABT-627</li> </ul>
Improvements in time to disease progression	<ul style="list-style-type: none"> <li>Cytostatic and cytotoxic agents offer the greatest promise for this benefit</li> </ul>

Our objective is to provide physicians and patients with a novel option for the treatment of hormone refractory prostate cancer, distinguish ABT-627 from current cytotoxic therapies and encourage the treatment of advanced prostate cancer patients currently only receiving hormonal therapy.

ABT-627 will be positioned as a physician and patient-friendly choice for advanced prostate cancer patients who have failed hormone therapy. ABT-627's novel mechanism of action provides a delay in disease progression and a positive impact on QOL. The oral, QD dosing enhances compliance and minimizes disruptions to daily living.

The message will focus on 3 key attributes:

- Efficacy (defined as increased time to tumor progression) in a patient group with few options
- Improvements in quality of life
- Convenience

Physicians no longer have to choose between *treating* advanced prostate cancer patients and a patient's quality of life. ABT-627 has a positive impact on disease progression and symptoms associated with quality of life, without the baggage of significant side-effects or the inconvenience of parenteral administration associated with current therapy choices.

This message expresses the key features of the agent in terms of patient benefits, as opposed to emphasizing the scientific/clinical aspects. Since prostate cancer is a terminal disease with a relatively long time for disease progression, the quality of a patient's life becomes even more critical. Especially in cancer treatment, where the therapy can often feel worse than the disease, the benefits that ABT-627 will bring, coupled with its benign side-effect profile, will have a significant impact on prostate cancer patients' lives.



### Clinical Studies

Phase II trials have been completed and the data are being analyzed. Preliminary results for the primary endpoint of time-to-disease progression and the secondary endpoint of time-to-PSA progression show that ABT-627 favorably delays both phenomena with a benign adverse event profile. The results are summarized below:

**Disease Progression:** The delay in median time-to-disease progression for evaluable subjects was improved by 52% and 43% for the 10mg and 2.5mg doses respectively over the placebo time-to-disease progression of 4.3 months.

**Time-to-PSA Increase:** A 150% and 150% improvement in median time-to-PSA progression for evaluable subjects was observed for the 10mg and 2.5mg doses respectively over the time-to-PSA progression placebo of 2 months.

Significant dose related decreases were observed in markers of metastatic bone disease.

### Key Prostate Cancer Competitors

Product	Company	Phase	Projected NDA Filing	Description	Anticipated impact on ABT-627
AG 3340	Agouron	III	2000	MMPI	In combination with mitoxantrone/prednisone. Unknown impact.
Marimastat	British Biotech	II	2001	MMPI	Side-effect profile significantly worse than ABT-627. Probably minimal impact.
SU 101	Sugen	I/II	2002	PDGF TK antagonist	Phase III in combination with mitoxantrone set to start in 1999. Uncertain impact.
AR 623	Aronex	II	2002	All-transretinoic acid	IV liposomal form of ATRA. HRPc trial began November 1998. Probably additive.
MGI 114	MGI Pharma	II	2002	Alkylating agent	Lead compound in acylfulvenes. Fairly toxic. Probably additive.
Liposomal Encapsulated doxorubicin	NeoPharm and P&U/Alza and others	II	2002	Anthracycline	Various forms being developed by various companies. Probably additive.
Sataraplatin	BMS	III	2000	Platinum complex	Oral platinum analog w/toxicities comparable to carboplatin. Probably additive.
Taxol	BMS	II	2001	taxane	In various combinations with other chemo agents. Probably additive.
Taxotere	RPR	II	2001	taxane	In various combinations with other chemo agents. Probably additive.

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ABT-594

**Descriptive Memorandum**

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**ABT-594 Opportunity Overview**

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Currently, there is an unmet market need for novel neuropathic pain treatments such as ABT-594. Therefore, this compound is likely to be well received in this arena. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

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**Market Size / Prevalence**

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

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**Competition, Current Marketed Products:**

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
<b>TOTAL</b>	<b>12.5</b>	<b>5.6%</b>	<b>N/A</b>	<b>N/A</b>
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
<b>TOTAL</b>	<b>\$351</b>	<b>21.7%</b>	<b>\$140</b>	<b>10.1%</b>
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

**Competition, Products in Development**

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

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Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through $\alpha 2\delta$ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

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Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

#### Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events.  Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimocloamol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

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## *Product / Development Background*

### *Scientific Rationale for ABT-594*

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

### *Clinical Studies*

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID, the maximum dose studied in this protocol. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients is anticipated to be included in the study.

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**Considerations****Target Profile:**

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

**Label Strategy:**

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
  - 2) Treatment of post-herpetic neuralgia
  - 3) Treatment of neuropathic pain
  - 4) Treatment of chronic pain
  - 5) Treatment of cancer pain

**Cost of Goods Sold:**

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

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*Pricing:*

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

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ABT - 751

**Descriptive Memorandum**

*February 2001*

Abbott Laboratories

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**JH 008174**

## ABT-751

### Opportunity Overview

Cytotoxic agents and hormones constitute the dominant classes of drugs available to treat cancer and are responsible for 96% of the total market. Since 1993, Taxol, a taxane developed and marketed by BMS, has been widely used. Another taxane, Taxotere, developed and marketed by Aventis, was launched in 1996. Combined worldwide sales of these two products were of nearly \$2 Billion US in 1999. Clinically, the development of drug resistance is the primary factor that limits the efficacy achievable with these drugs.

Abbott's anti-mitotic agent (ABT-751) is a novel, oral cytotoxic agent that acts by a mechanism similar to that of the taxanes but retains activity against taxane resistant cells. ABT-751 binds to the colchicine site on tubulin and inhibits the *in vitro* polymerization of microtubules. The interference with normal microtubule dynamics leads to a block in the cell cycle at the G2/M phase that ultimately results in the induction of cellular apoptosis. ABT-751 is a potent antimitotic agent that inhibits the proliferation of a broad spectrum of human tumor derived cell lines including those that are paclitaxel and doxorubicin resistant due to the multidrug-resistant (MDR) phenotype or other genetic changes.

ABT-751 demonstrated impressive oral antitumor activity when evaluated in both synegeic and human xenograft tumor models. The antitumor response was independent of the MDR status of the model, consistent with the activity observed in cell cultures. In sharp contrast with other cytotoxic drugs, the maximum tolerated dosage of ABT-751, on a q.d. 1-5 schedule, could be administered for an extended period (q.d. 1-21 or q.d. 1-28) resulting in a dramatic enhancement of the antitumor activity. These results suggest that the colchicine site ligands, such as ABT-751, will exhibit a broad spectrum of activity that will be distinct from that of other classes of antimitotic drugs. Oral availability of the compound is high. Taxol and Taxotere, in contrast, have no oral bioavailability.

The most significant finding in toxicology studies was a change in systemic and pulmonary vascular resistance following intravenous infusion of ABT-751 to anesthetized dogs. These effects led to an inverse response in cardiac output. Similar changes were observed following infusion of a structurally unrelated colchicine-site ligand, and therefore most likely represent a class effect. Additional toxicology studies focusing on vascular pathology will be performed to further elucidate this finding.

ABT-751 was administered to patients with advanced cancer in Japan in a Phase I study. Toxicities seen after single doses and 5 days of q.d. dosing were nausea, vomiting, diarrhea, epigastric pain, ileus and peripheral neuropathy. Grade 2 toxicity was peripheral neuropathy and associated paresthesias. Pharmacokinetic analyses showed plasma concentrations equivalent to those that affected systemic resistance and cardiac output in the anesthetized dog study. However, no adverse cardiovascular effects were observed in the Japanese Phase I trial. Evidence of ABT-751 efficacy was exhibited in one patient with uterine sarcoma, one patient with NSCLC after single doses, one patient with gastric cancer and one patient with uterine cervical carcinoma demonstrated decreased tumor markers after repeated dosing.

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The planned initial Phase I study in the U.S. will determine the maximum tolerated dose and dose-limiting toxicities of ABT-751 given orally once a day or twice daily for multiple cycles in patients with advanced malignancies. In addition, pharmacokinetics in a western population, and optimal dose and schedule will be determined. Phase II studies will be initiated in patients with different cancer types:

- Refractory breast (taxane failures)
- Hormone refractory prostate
- Bladder
- Lung
- Cervical
- Hepatocellular
- Other possibilities: colorectal, sarcoma, renal cell, pancreatic, HNSCC

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

This growth of the cytotoxic segment has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Uptake of these newer agents, however, can be dependent on the cost sensitivity of the local market.

The clinical targets identified for this compound include late stage breast cancer, late stage NSCL cancer (on-label), with late stage ovarian and pancreatic cancer as additional cancer types where efficacy has been demonstrated, but not filed. This product may also be potentially efficacious in cancers such as gastric, colorectal, prostate, bladder, esophageal, hepatocellular (ex US), lymphoma, and leukemia. Targets will be refined as we know more about this compound's in-vivo activity.

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The following tables summarize the key competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytosan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

#### *Compounds in Development*

ABT-751 induces a mitotic block by binding to the colchicine site on tubulin and thereby affecting tubulin polymerization. There are no currently available drugs which function by the mechanism described above. However, vinca alkaloids and taxanes fall into the broad category of anti-mitotics although they produce the anti-mitotic effect through different mechanisms. The following table summarizes anti-mitotic compounds in development.

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Company	Compound	Indication	Status of compound	Status of project
<b>Colchicine-site ligands</b>				
Oxigene	combretastatin-A4 phosphate	Tumor vasculature	Phase I	active
Tularik	T138607 (phosphate prodrug)	Cancer (unspecified)	Phase I	active
Tularik	T900607	Cancer (unspecified)	Preclinical	active
ICI/CRC	Amphethinile	Cancer (unspecified)	Phase I (abandoned 1988)	inactive
Wellcome Research	1069C	Cancer (unspecified)	Phase I (abandoned 1996)	inactive
NIH	Trimethylcolchicinic acid	Various tumors	Phase I (1990, abandoned)	inactive
Parke-Davis	CI-980	ovarian, colorectal	Phase II (abandoned 2000)	inactive
<b>Vinca alkaloid-site ligands</b>				
BASF	LU103793 (dolastatin 15 analog)	Cancer (unspecified)	Phase II (abandoned)	active
Servier	Vinxaltine	Cancer (unspecified)	Phase I	unknown
NCI	dolastatin 10	Adv. Cancers	Phase I	unknown
Teikoku Hormone	TZT-1027 (dolastatin 10 analog)	Cancer (unspecified)	Phase I (Jpn)	unknown
Lilly	LY 355703 (cryptophycin 52)	Cancer (unspecified)	Preclinical	unknown
Takeda	Maitansine	Cancer (unspecified)	Preclinical	unknown
<b>Microtubule stabilizing agents (non-taxanes)</b>				
Soc. Biotech. Res/ Bristol-Myers Squibb	Epothilone	Cancer (unspecified)	Preclinical	active
Bristol-Myers Squibb	eleutherobin	Cancer (unspecified)	Preclinical	active
Pharmacia & Upjohn	sarcodictyins	Cancer (unspecified)	Preclinical	active
Takeda	GS-164	Cancer (unspecified)	Preclinical	active

The novelty of this mechanism offers the promise of differentiation that will diminish the threat from potential competitors. However, this novelty is balanced by the similarity to current mechanisms, such as taxanes and vinca alkaloids, which suggests the promise of clinical efficacy. With the opportunity to be first or second to market with an agent that binds to the colchicine site, the competitive situation seems modest.

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ABT – 492

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**ABT 492****Overview**

The commercial success of fluoroquinolones such as ciprofloxacin and levofloxacin, along with the desire to further improve the properties of these compounds (microbiological spectrum and safety, for example) has led to fierce competition to identify analogs with superior therapeutic properties. In addition, the development of resistance to present antibiotics will drive a continued need for new agents. Goals for a quinolone antibiotic include broad-spectrum indications equal to trovafloxacin, antibacterial activity comparable to trovafloxacin, tolerability comparable to levofloxacin, oral and intravenous formulations, once daily dosing, length of treatment equal to moxifloxacin, and an acceptable cost of goods. ABT-492, an in-licensed compound from the Wakunaga Pharmaceutical Co., is being developed for evaluation to meet these goals:

The *in vitro* antibacterial activity of ABT-492 was consistently more potent than trovafloxacin against most quinolone-susceptible pathogens, including species responsible for community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. The compound has potent activity against multidrug-resistant *S. pneumoniae* (penicillin-, macrolide-, tetracycline-resistant) and retained activity against *S. pneumoniae* strains resistant to other quinolones including trovafloxacin. ABT-492 was also highly active against anaerobes and ciprofloxacin-susceptible *P. aeruginosa*. ABT-492 was as active as trovafloxacin against *C. trachomatis*, indicating good intracellular penetration. Thus, ABT-492 is likely to be a useful broad-spectrum antibacterial agent. The enhanced antibacterial activity of ABT-492 relative to ciprofloxacin, levofloxacin, and trovafloxacin is likely to be explained, in part, by its potent interactions with bacterial topoisomerases. ABT-492's equivalent activity against both the DNA gyrase and the topoisomerase IV of pathogens, give ABT-492 a potential for decreased development of resistance.

The *in vitro* potency data suggests that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin and superior to levofloxacin. In addition, ABT-492 was consistently more potent than trovafloxacin against MRSA and vancomycin-resistant enterococci. In both these cases, however, therapeutic utility remains to be assessed in the clinical setting.

*S. pneumoniae* was chosen as the dose-defining pathogen since it is the key pathogen in severe respiratory tract infections and treatment of infections caused by this pathogen has traditionally been a weakness of most quinolones. For treatment of fluoroquinolone-susceptible *S. pneumoniae* respiratory tract infections, oral dosing may be similar to trovafloxacin based on data generated in lung infection models. Because of the excellent potency of ABT-492 against fluoroquinolone-resistant *S. pneumoniae* with an MIC<sub>90</sub> of 0.12 µg/ml, this group of emerging strains may be targeted as a key differentiation point from other quinolones. Also, data from the thigh infection model suggests significantly greater efficacy for ABT-492 than for trovafloxacin.

**The Market**

ABT-492 is broad-spectrum anti-infective agent with potential application across a broad range of indications, including respiratory infections, genito-urinary infections, and skin/soft tissue infections. It is assumed that a pediatric formulation would not be a part of the primary development plan due to the known adverse events caused by quinolones in pediatric populations. Nonetheless, reports of quinolone pediatric development has been reported (gatifloxacin), hence the pediatric market should be regarded as a potential upside for this quinolone should its safety profile merit its use in pediatrics.

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**Current Treatment Options**

Class	Mechanism of Action	Comments
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance.
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains and modification of penicillin-binding proteins.
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; <i>H. flu</i> activity continues to be class weakness, along with GI adverse events, drug-drug interactions, & taste perversion
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in a broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram- profile will be used primarily in nosocomial setting

**U.S. Market**

1999 U.S. antibiotic prescription and sales data are presented in the table below.

			1995	1996	1997	1998	1999	CAGR <sub>95-99</sub>
U.S.	TRXs (MM)	Tab/Cap	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap	\$4,057	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The IV market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

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Quinolones have seen dramatic growth, with oral and IV sales growing at 17% and 16% compound annual rates, respectively, from 1995-1999. This growth is a function of the newer quinolones successfully penetrating the RTI segment, which was initiated with the 1997 launches of Levaquin and Trovan (withdrawn) and continues with the recent introductions of Tequin and Avelox.

#### Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. The tab/cap represents the largest segment, with sales of \$9.4 billion on 770 MM TRX. TRX growth has been flat, with a 1996-99 CAGR of 0.5%; the use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-US, the quinolone class accounted for 8% (62MM) of total tab/cap market prescriptions and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-US, with approximately 47% of the quinolone market Rx's (29MM) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market, and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-US levofloxacin sales (\$370MM).

1999 Ex-US Tab/Cap Market						
Class	Sales (\$MM)	Sales Share	Sales CAGR '96-'99	TRXs (MM)	TRX Share	TRX CAGR '96-'99
Market	\$9,348	-	3.6%	770	-	0.8%
Quinolone Class	\$1219	13%	-12%	62	8%	NA
Cipro	\$530	5.7%	4.9%	29	3.8%	NA
Levaquin	\$466	5.0%	NA	18	2.3%	NA
Trovan	\$12	0.1%	NA	0.5	0.1%	NA

#### *Competition*

The anti-infective pipeline is very competitive, but most of the competition is focused on improving the activity and safety of the quinolones. Ketolide development is the only other area of activity which is in late stage of development. The quinolone compounds in present development may fall out because of safety or lack of activity against resistant pathogens.

Competitive Analysis - Emerging Competition					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Ketek (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.

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Competitive Analysis – Emerging Competition					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to quinolones for MRSA; highly potent vs. RTI pathogens <i>H. flu</i> , <i>M. cat</i> , and <i>S. pneumo</i> and UTI pathogens <i>E. coli</i> and <i>P. mirabilis</i> , CRSP; potency > spar, trov, grepa and $\geq$ moxi; activity vs. <i>P. aeruginosa</i> ?; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; 700 patient database
Sitafloxacin	Daiichi Seiyaku	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Very potent MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC; will likely be target to severe rather than community infections
Ecenofloxacin	Chiel Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to lome and oflo vs. <i>P. aeruginosa</i> . $t_{1/2}$ = 14-19 hr; will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G+/-; excellent activity against <i>H. flu</i> , <i>c. jejuni</i> , <i>M. pneumo</i> , and <i>C. trachomatis</i> ; greater potency than cipro; $t_{1/2}$ ~7 hr; BA~80%
T-3811	Toyama/BMS	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency $\geq$ trova, STFX & HSR-903

#### Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

ABT-492 is one of the most active agents against the resistant organisms. It has indications that will have a low propensity for the development of resistance. ABT-492 will be developed to maximize any opportunities to shorten therapy. ABT-492 was chosen from hundreds of quinolones because of its potential to be well tolerated and safe in humans. ABT-492 will have few interactions with other drugs.

Unmet Need	Pipeline Impact
Activity against resistant organisms	<i>Strep. pneumo</i> , MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant <i>Strep. pneumo</i> strains; quinolone-resistant <i>Strep. pneumo</i> may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety

	profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

#### Considerations

**Product Usage:** Physicians are likely to use ABT-492 for the sicker patients with the most difficult infections to treat. In the outpatient arena it will be used to treat community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis in the older patients with an underlying illness. It will also be used in the hospital for the community-acquired pneumonia patient who requires hospitalization and for serious nosocomial infections.

While many regard quinolones as agents that should be reserved for 2<sup>nd</sup> line use, their activity against *H. influenzae* and resistant *Strep. pneumoniae* (which current macrolides do not offer) have resulted in a high level of acceptance for empiric 1<sup>st</sup> line use. The improved safety profiles of several recent quinolones have facilitated their use as 1<sup>st</sup> line agents. Provided that ABT-492 is proven to have a benign safety/adverse event profile, it will likely receive usage in both 1<sup>st</sup>-line (non-severe) and 2<sup>nd</sup>-line (severe) infections.

**Side Effects:** The quinolone class has potential prolongation of the QT interval and other cardiovascular effects. There is also increased regulatory scrutiny due to recent quinolone withdrawals from international markets. ABT-492 has been evaluated in the standard *in vivo* models used to evaluate QT interval potentials of other antibiotics and has shown no evidence of increasing QT. Also, compared to marketed quinolones, preclinical studies show no evidence or no increase incidence of CNS drug concentration (ie: less potential for dizziness); phototoxicity; and liver toxicity.

**Off-label use:** It is difficult to predict at this time what off-label uses will be seen for this compound. Initial development will be for the more common respiratory, urinary tract, skin, and hospital infections. Other indications will be evaluated after the primary approval of this compound. Many of the secondary indications will get usage before we have regulatory approval.

**COGS:** The initial cost of goods is in \$6000/kg range, but will come down rapidly after the initial starting materials are determined. At time of launch ABT-492 will have a cost of goods in the \$1500/kg range which is competitive compared to other quinolones and other new antibiotics.

**Dosing:** Based on animal models and the *in vitro* activity of ABT-492 the dose for most oral indications will be in the range of 100 to 200 mg give once daily.

**Development/Regulatory.** Anti-infective compounds are well understood by regulatory agencies globally and they have clearly defined clinical development path and regulatory guidelines for reference. Abbott Laboratories has been in this arena for many years and has experience with the FDA and European regulatory agencies and so the hurdles to development are well known. ABT-492 has begun but not yet completed its first Phase I study in healthy volunteers.

**Other Approaches:** Because of the well defined development guidelines there are not many options. The major development options are in dosing regimens. ABT-492 is a very potent drug which has demonstrated rapid killing of pathogens *in vitro* and *in vivo*, and the development plan will attempt to shorten treatment durations to increase the competitive advantages of this activity.

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*Pricing:* The community infection market is quite competitive from a pricing standpoint, with recent quinolones priced at approximately \$45 per 5-7 days of therapy. The pricing strategy will depend on strengths/weaknesses of the ABT-492 product label, the competitive landscape at launch, and the managed care environment, but current pricing assumption is parity for ABT-492 with respect to other quinolones.

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**ABT 510****Overview**

There is abundant evidence that primary tumor growth and metastatic progression require new blood vessel formation (angiogenesis). Tumors secrete inducer proteins including bFGF and VEGF that activate microvascular endothelial cells (EC) causing them to proliferate, migrate and organize into capillary structures. Activated endothelial cells also enhance malignant progression by producing signal molecules (cytokines) that inhibit programmed cell death (apoptosis) of tumor cells. Since anti-angiogenic therapy targets genetically stable endothelial cells, resistance typically seen following cytotoxic chemotherapy is not observed. Moreover, angiogenesis inhibitors should not have the intrinsic toxicity of anti-proliferative chemotherapy. Angiogenesis is also a feature of several other pathophysiologic states of large unmet medical need (macular degeneration, psoriasis, and arthritis, among others).

Angiogenesis sustains the growth and progression of tumors. Unlike chemotherapy or radiation, both of which can damage normal cells in addition to tumor cells, anti-angiogenic agents are hypothesized to prevent growth of new blood vessels and to disrupt critical tumor survival signals produced by EC. These agents may keep tumors in a dormant state for as long as the compound is administered and tumor regressions may occur. Proof of this principle has been demonstrated in pre-clinical models. Currently, at least thirteen compounds with anti-angiogenic activity in cancer are in various phases of clinical development, however few act directly and specifically on the angiogenesis process. Anti-angiogenesis drugs are not expected to replace or compete with current therapies. Instead, if these agents prove to be effective, it is believed that they will be used as supplemental therapy to prevent metastasis following surgery, cytotoxic chemotherapy or radiotherapy. As for cases where tumors have already metastasized, these agents could slow down disease progression and maintain "disease dormancy".

Thrombospondin-1 (TSP-1) was the first natural angiogenesis inhibitor to be discovered. TSP-1 is a large, multifunctional protein. TSP-1 rapidly inhibits EC migration and increases EC apoptosis through activation of caspase-3-like proteases. The normal tissue expression of TSP-1 limits inappropriate neovascularization, however it is transcriptionally activated by the tumor suppressor gene product p53. Therefore, TSP-1 is down-regulated and under-produced in p53 defective tumors. In rodent models, ectopic overexpression of TSP-1 inhibits the malignant phenotype as does direct administration of TSP-1 in the circulation. However, direct clinical use of TSP-1 is not feasible because of its scarcity, large size and multiple other biological functions.

The angiogenic activity of TSP-1 has been localized to the 50,000 MW N-terminal stalk region of this protein, and more specifically to the properdin (Type-1) repeats within this region. Although small synthetic peptides within this region have only weak antiangiogenic activity, it was discovered that a single D-amino acid replacement in a properdin region peptide led to an increase in activity of greater than 1000-fold. ABT-510 is a parenterally available nonapeptide. Although ABT-510 competes with TSP-1 for binding to the EC, the exact mechanism of anti-angiogenesis is unknown.

ABT 510 is supplied for clinical use as a sterile solution in acetate salt in 5% dextrose. ABT 510 is soluble and stable in water.

In vitro, ABT 510 inhibits chemotactic VEGF/bFGF-stimulated migration of human microvascular endothelial cells (EC) with an IC<sub>50</sub> of approximately 0.250 nM. This effect is EC specific. ABT-510 (10mg/kg/day subcutaneously) blocks VEGF-induced corneal vascularization in mice. It potently and selectively competes with TSP-1, binding the CD 36 receptor.

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ABT 510 inhibits tumor progression in vivo. ABT 510 (20mg/kg/day subcutaneous administration) inhibited tumor progression (78% growth inhibition at day 38) in a model of human breast cancer (MDA-MB-435) growing in the breast pads of nude mice. Dose dependent inhibition of B16F10 melanoma lung metastases was observed in a second murine model. ABT 526, a molecule highly similar to ABT 510 (which was not advanced into human trials because of concatamer formation) was administered to 23 companion dogs (25mg SQ BID) with sporadic cancers (head and neck carcinoma, lymphoma, sarcoma, etc) refractory to conventional chemotherapy. Surprisingly, 2 complete responses, 5 partial responses ( $\geq 50\%$  shrinkage) and 6 cases of disease stabilization were observed.

Assays for toxicity, histamine release, hemolysis, T-cell function neutrophil migration, platelet aggregation, receptor (CEREP) screening and CNS function were unremarkable. ABT-510 produced no physiologically significant changes in cardiovascular or hemodynamic function in anesthetized dogs. In addition, there were no physiologically significant changes in clinical blood chemistry profiles or cardiac electrophysiologic function in response to ABT-510. Doses that were many times higher than the predicted efficacious concentration produced a moderate reduction in mean arterial blood pressure in conscious monkeys. ABT-510 was not mutagenic in the Ames assay. It is concluded therefore that ABT-510 has an excellent pre-clinical safety profile.

ABT-510 is currently in Phase I clinical trials. Because of its exceptional safety profile, normal volunteers are being dosed with ABT-510 to establish human safety and pharmacokinetic parameters. Review of these data will lead to a Go/NoGo decision for Phase II trials in the Summer of 2001.

#### *The market*

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market. The market for products to treat cancer is changing rapidly. It is a growing market fueled by:

- Increasing disease incidence
- New product entries
- New therapeutic paradigms
- A growing adjunctive market, which increases the number of patients eligible for chemotherapy
- Intense research and competition

The increase in the aging population in developed countries increases the incidence of cancer. The diagnosed cancer incidence and prevalence in seven major markets, including the U.S., France, Germany, Italy, Spain, U.K. and Japan are close to 3 million and 10 million respectively. The numbers are increasing steadily. Currently, about one-third of the new medicines in development are targeted against cancer.

Cancer is not a single disease, but includes more than 100 different disorders, which have at their core uncontrolled cell growth. Of these disorders, the cancer types that offer the greatest commercial opportunity include breast, colorectal, lung, ovarian and prostate (based on incidence/prevalence/unmet need). Treatment of breast, lung and prostate cancers account for more than 50 percent of the direct medical costs of cancer therapies. Other cancer types, specific to one or more of the major international markets, may provide niche opportunities. For instance, stomach (gastric) cancer is relatively common in Japan but not in the U.S. or Europe; similarly, liver cancer has a greater occurrence in Japan, Italy and Spain.

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# PART 5

Depending on tumor type, cancer can be treated with surgery, radiation, chemotherapy (cytotoxic), hormonal therapy or a combination of any of these. For the purpose of this analysis, we will define the cancer market as chemotherapeutics and the adjunctive therapies used to counter the effects of chemotherapy and radiation therapy. The following charts summarize the global sales for these products.

#### Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
Hormone	4,414	4,784	4,884	5.2%
Cytotoxic	4,278	5,212	6,268	21.0%
Adjunctive	3,367	3,651	4,166	11.2%
Total	12,059	13,647	15,318	12.7%

Source: Datamonitor

#### Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
US	5,564	6,276	7,422	15.5%
Ex- US	6,495	7,370	7,896	10.3%

Source: Datamonitor

#### *Chemotherapeutic agents*

*Cytotoxic therapies* include classes such as alkylating agents, anti-tumor antibiotics, anti-metabolites and antimitotics (taxanes). These agents are toxic and demonstrate dose-limiting side effects. The commercial value of this segment is significantly understated, as most of the products are available in generic form.

The growth of the cytotoxic segment in the past three years has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Utilization of these newer agents, however, appears to be dependent on the cost sensitivity of the local market. For example, secondary sources indicate that Taxol has recorded over 60% of its global sales in the US market alone and is prescribed with far less frequency in the more cost sensitive UK, German and French markets.

Most chemotherapeutic agents are indicated for just one or two cancer types, but get significant off-label use once approved. Up to 60% of an oncology product's use is potentially for off-label indications. Much of this use is driven by the publication of data and/or approvals in other countries.

#### *Hormonal therapies*

Of the top-selling drugs in each major geographical region, *hormone therapies* contribute approximately one-third of the sales ex-US and one-fourth in the US. Hormone therapies for the treatment of cancer include Lupron (leuprolide/TAP), Zoladex (goserelin/Zeneca), Nolvadex (tamoxifen/Zeneca) and other agents used to treat hormone responsive diseases such as prostate and breast cancer. These agents are generally administered chronically and have reduced side effects compared to cytotoxic therapies. Sales of this category are driven primarily by Lupron and Zoladex. The US market has become increasingly cost sensitive in the Medicare sector, which accounts for over 70% of Lupron sales.

#### *Adjunctive agents*

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The availability of effective *adjunctive agents* also allows the cytotoxic chemotherapeutic agents to be administered at higher doses and/or more frequently, or used in a more palliative role, since the adjunctive therapies can reduce the impact of the chemotherapy on the patient's quality of life. Agents in this class include immunostimulants, anti-emetics and bisphosphonates. The growth of this market is linked to the growth of the cytotoxic market, as the increased use of cytotoxic agents drives an increased use in adjunctive therapy. The highest selling product in this class is Neupogen (filgrastim/Amgen) with 1998 sales of over \$1 billion.

#### *Biologic Therapy*

New therapies under development offer the promise of fulfilling several unmet needs in the treatment of cancer. Experts have predicted that in the future early therapy for breast cancer will be dominated by biological approaches, such as monoclonal antibodies (Herceptin/Genentech), which is widely thought to have strong market potential. Genentech recently reported strong second quarter sales of the product in the US of \$46.2 million, and it is estimated that if only half of US women with breast cancer who over-express this gene received Herceptin, sales would top \$600 million. In addition to monoclonal antibodies, other biological approaches include vaccines and gene therapy.

#### *Future Trends*

Emerging science in the past decade offers the potential to radically alter the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. New therapies offer the promise of fulfilling several unmet needs in the treatment of cancer. These include matrix metalloproteinase inhibitors (MMPis), continued expansion of biologics, photodynamic therapies (PDT), anti-angiogenics, and multiple drug resistance (MDR) modifiers. This market does not yet exist, though success of "cytostatic-like" treatments, such as hormonal therapies for prostate and breast cancer, suggests that the market potential for cytostatic agents could be significant.

#### *Competition*

The angiogenesis pipeline is very competitive, but this level of intensity is somewhat skewed by the large number of mechanistic approaches that are being claimed to demonstrate angiogenic activity. Furthermore, clear evidence of efficacy for these agents has not yet been demonstrated. For the purposes of this summary, only those compounds considered true anti-angiogenic compounds have been included. Companies with compounds in clinical development include Genentech, Entremed, Sugen, TAP, Magainin and Pharmacia Upjohn.

#### **Angiogenesis Compounds in Clinical Development**

Compound	Indications	Company	Phase
Neovastat	Solid tumors	Aetema	III
RhuMab VEGF	Cancer	Genentech	II/III
Vitaxin	Arthritis, psoriasis, CVR	Ixsys	II
SU-5416	Cancer	Sugen	II/III
TNP 470	Cancer, arthritis	TAP	II
Thalidomide	Cancer	EntreMed/BMS	I
Squalamine, squalus	Cancer	Magainin	I
RPI 4610	Cancer	Ribozyme	I
VEGF antagonist	Cancer, retinopathy	NeXstar	I
Angiostatin/Endostatin	Cancer	EntreMed	I

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### *Unmet Needs*

Cancer remains the second leading cause of death in the United States, Europe and Japan, and consequently, offers an attractive market opportunity for the pharmaceutical and biotechnology industries. This year about 563,100 Americans are expected to die of cancer, more than 1,500 people a day. In the US, 1 or 4 deaths is due to some form of cancer. In 1999, about 1,221,800 new cancer cases are expected to be diagnosed.

For most cancers, the level of physician satisfaction with current therapies is low. It has long been recognized by researchers, physicians, patients and family members that current treatment options may often be as devastating as the underlying disease.

Unmet needs in this market vary by tumor types and stages, with some tumors responding to treatment with better mortality and/or morbidity results than others. However, cancer is still treated as a terminal illness with significant shortcomings in present treatments. In general, unmet needs include:

<b>Need</b>	<b>ABT-510 Attribute</b>
Enhanced efficacy of therapeutic agents	Potential for enhanced efficacy
Reduced toxicity	Potential for reduced toxicity over current cytotoxic treatment
Improvements in drug administration	TBD
Improved target delivery of cytotoxics and novel therapeutics	Unknown
Proven outcomes data	Quality of Life and Pharmacoeconomics to be assessed

### *Considerations*

**Product Usage:** Physicians have indicated that they would use anti-angiogenic agents initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. Anti-angiogenesis agents are regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy. Of course, their ultimate use will depend on the benefit provided, which cannot be determined until clinical trials have been completed. Efficacy evidence in humans manifested by tumor response of the magnitude seen in the preliminary dog studies would stimulate tremendous enthusiasm in the oncology community.

**Product Benefits/Efficacy:** Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. There is a great deal of enthusiasm for this mechanism in the scientific and lay audience. The concept is very intuitive. Products, such as ABT-510, that promise a clinical benefit without the usual toxic trade-offs associated with current chemotherapeutic agents, will be enthusiastically received by oncologists.

**Side Effects** The proposed safety profile of anti-angiogenic agents may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, anti-angiogenic agents may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance.

*Off-label use:* Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

*Other indications:* ABT-510 may be effective in other therapeutic roles, such as arthritic diseases and macular degeneration. These other indications may offer a commercial upside, through internal development or co-development/out-licensing opportunities.

*Competition:* While there are a relatively large number of angiogenesis inhibitors in development, it is unclear whether they will demonstrate a superior efficacy or side-effect profile vs. ABT-510. The mechanism of angiogenesis suggests that multiple anti-angiogenic approaches may be required to maximize the clinical benefit.

*COGS:* Initial estimates on finished cost of drug place it in the range of Lupron costs. Depending on final dosing requirements, the cost of this compound could become a significant obstacle. However, this will need to be considered in light of the pricing flexibility in the oncology market, where there is limited pricing sensitivity for products that are reimbursed. Any financial analysis will need to include royalty obligations to Northwestern University.

*Dosing:* There is still some uncertainty regarding the route of administration and feasible dosage forms for ABT-510. An "inconvenient" formulation leaves this product extremely vulnerable to competitors with more convenient dosage forms. A convenient dosage form, such as a monthly depot, will enhance product adoption over a less convenient form. However, the effect of the various dosage forms on product adoption will be dependent on the benefits the compound provides, side-effect profile and availability of competitive agents with more convenient dosage forms. For chronic therapy, convenience will play an important role in market penetration, given alternative agents. Although less convenient than oral therapy, parenteral therapy (depot, but not self-administered sub-cutaneous) is currently reimbursed by Medicare in the US. Over 60% of all cancer patients have Medicare as their primary healthcare coverage in the US.

*Development/Regulatory:* With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several anti-angiogenic agents in late stage development, Abbott can learn from their experience.

*Other Approaches:* Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

*Pricing:* The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

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**ABT - 518**

**Descriptive Memorandum**

*February 2001*

**Abbott Laboratories**

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**MMPI****Overview**

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

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demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

#### *The market*

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

**Global Sales by Market Segment (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

**Sales by Region (\$ MM)**

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPi will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPis will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

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The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

#### *Compounds in Development*

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3<sup>rd</sup> or 4<sup>th</sup> to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPis in Clinical Development for Cancer

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Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

#### *Product profile*

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

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	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of	Provides more than one of the efficacy benefits outlined.

	<p>the following benefits in at least one solid tumor type:</p> <ul style="list-style-type: none"> <li>• Increased survival</li> <li>• Tumor regression</li> <li>• Improved quality of life</li> <li>• Increased time to tumor/disease progression</li> </ul>	
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPI agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

#### *Marketing overview*

*Product Usage:* Physicians have indicated that they would use MMPIs initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPI was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

*Product Benefits/Efficacy:* Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPI mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

*Side Effects:* The proposed safety profile of MMPIs (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPIs may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3<sup>rd</sup> or 4<sup>th</sup> MMPI to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

*Dosing:* Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

*COGS:* Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

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*Off-label use:* Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

*Competition:* As the 3<sup>rd</sup> or 4<sup>th</sup> MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

*Development/Regulatory:* With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

*Other Approaches:* Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

*Pricing:* The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

*Dosing:* Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

#### *Clinical Studies*

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

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# Farnesyltransferase Inhibitor

## Descriptive Memorandum

*February 2001*

Abbott Laboratories

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**JH 008200**

## Overview

The Ras genes were the first oncogenes of mammalian origin to be discovered. Intensive research over the last decade has led to the elucidation of the normal function of cellular Ras protein, the role of Ras mutations in oncogenic transformation, and the identification of molecular targets, such as the enzyme farnesyltransferase, for inhibiting Ras activity. Although farnesyltransferase inhibitors (FTIs) were initially designed with the intention of inhibiting the posttranslational prenylation, and hence function, of Ras, it is now becoming apparent that farnesylated proteins other than Ras (e.g., RhoB) are also critical for malignant growth and may be the relevant target for inhibition of farnesylation. While it remains controversial whether blocking Ras activity or altering the RhoB prenylation status is the actual function of an FTI, these agents, exemplified by ABT-839 and FTIs in the clinic, exhibit remarkable anticancer activity against a wide variety of tumors in preclinical models. The current FTI program is projected to reach DDC status in January, 2001.

Abbott evaluated one FTI, ABT-839, in normal volunteers, but decided to discontinue development of this drug due to its poor pharmacokinetic profile. Invaluable experience was gained, however, from both the preclinical and clinical studies with this compound. Abbott's second-generation series are novel structures that exhibit significantly improved potency and oral bioavailability.

There continues to be tremendous enthusiasm in the medical community and pharmaceutical industry for this mechanism of action. Farnesyltransferase inhibitors have demonstrated impressive antitumor activity in preclinical models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at the maximal tolerated dose. These agents appear to inhibit angiogenesis and, consistent with this activity, minimal resistance has been observed in preclinical models. The potential also exists for synergistic activity in combination with cytotoxic chemotherapy.

## The market

Cancer remains the second leading cause of death in the US, and consequently is an attractive market opportunity for the pharmaceutical/biotechnology industries. Approximately 40% of all Americans will develop cancer in their lifetime.

The worldwide cytotoxic and hormonal cancer therapies market is highly fragmented with only BMS and Zeneca holding a greater than 10% market share. Although the market is not concentrated, the field is highly competitive with more than 60 companies focused on the cancer research area. The growth of the oncology market is fueled by increasing disease incidence, new product entries, new therapeutic approaches, a growing adjunct therapy market that expands the number of patients eligible for chemotherapy, and intensified research competition. The data in Tables 1 and 2 summarize the value of the current oncology market. A great deal of uncertainty surrounds the concept of cytostatic treatment of cancer. Conceptually it may transform the way cancer is treated, allowing patients longer disease free survival and improved quality of life. However, at this point in development, this paradigm does not exist in cancer. Considering market, clinical and patient dynamics factors, breast, colorectal, prostate and non-small cell lung cancers are the most attractive targets for development.

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Table 1. Global sales by market segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Table 2. Sales by region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex-US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the FTI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, FTIs will probably be adopted initially as add-ons to current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

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## Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

## Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

## Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Emerging science within the past decade has radically altered the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. Abbott has multiple discovery cytostatic targets, which may improve effective, but we are not alone: more than 200 compounds from other players are in development. The goal of cytostatic therapy is to improve quality of life, controlling the disease and transforming aggressive treatment to a chronic condition, which has been compared to the impact of protease inhibitors on the course of HIV.

*Clinical Studies*

Considering all the factors, market, clinical and patient dynamics, breast, colorectal, prostate and non-small cell lung cancer appear to be the most attractive targets for development. The development of cytostatic agents faces a number of challenges as regulatory agencies and physicians evaluate the new emerging paradigm of cancer therapy.

Despite the enormous medical need, drugs for chronic treatment/disease stabilization and improved quality of life for cancer patients do not yet exist. Correspondingly, animal models test efficacy that has not yet been validated as predictive of response in humans. Medical oncologists have historically depended on determination of maximum tolerated dose and response manifested by tumor shrinkage for cancer drug development. These parameters are not relevant to novel "cytostatic" agents. Combination with conventional cytotoxic drugs will be required in the near term and will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.

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Competition:Within Project Approach

Company	Compound	Indication	Status of compound	Status of project
Janssen Pharmaceutica	R-11577 (A-251076)	Cancer (unspecified)	Phase III	active
Schering-Plough	Sch66336 (A-285622)	Cancer (unspecified)	Phase II	active
Merck	L-778123	Cancer (unspecified)	Phase I (i.v.) abandoned	unknown
Bristol-Myers Squibb	BMS-214662	Cancer (unspecified)	Phase I	active
LG Chemical	LB 42908	Cancer (unspecified)	preclinical	active
Rhône-Poulenc Rorer	quinuclidine derivatives	Cancer (unspecified)	preclinical	active
Pfizer	unknown structure	Cancer (unspecified)	preclinical	active
Parke-Davis	unknown structure	Cancer (unspecified)	preclinical	active
Roche	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Eisai	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Banyu	FPP mimetic	Cancer (unspecified)	preclinical	unknown
ISIS	ISIS-2503 (ras antisense)	Cancer (unspecified)	Phase I	active

Within Therapeutic Area

Approach	Selected Compounds	Company(ies)	Status
antisense	ISIS 3521, ISIS, 5132	ISIS	phase I
cytotoxic agents	camplosar, CI-980, farestroon, Genzar, Hycamtin, Indarubicin, Novantrone, Onconase, Capecitabine, Tomudex	P&U, Warner-Lambert, Schering, Lilly, SKB, P&U, Immunex, Alfacell, Roche, Zeneca	most phase III
differentiation	targretin, panretin, 5-azacytidine	Ligand, NCI	Ligand in phase II/III
drug resistance modifiers	VX-710, 776C85, RMP-7, CT-2584	Vertex, Glaxo Wellcome, Alkermes, Cell Therapeutics	Vertex in phase II
gene therapy	Onyx-015, , MDRx1, GLI-328, IL-2, GV-1301	Onyx, Introgen, Therion Biologics, Theragen, Genetic Therapy, Cyclacel, RPR Gencell, GeneMedicine, Titan, etc	Restricted to accessible cancers. Most advanced: Phase I/II
hormonal therapy	Zolodex, amideox, droloxifen, Oncolar, Rivizor, Casodex, rogletimide	Zeneca, Pfizer, Novartis, Janssen, US bioscience	most phase III
immunotherapy			
antibodies	IDEC-Y2/In2B8, anti-HER2, anti EGFR	IDEC, Genetech, ImClone	IDEC recently approved, others phase III
cytokines	IL-12, IL-4, Proteukin, Roferon-A	Roche, Schering, Chiron, Roche	phase III
vaccines	rV-gp100, Genevax, MGv	Apollon, Therion, Progenics	phase I, II
photodynamic	photofrin, promycin	QLT photo, Vion	phase III
radiation sensitizers	Neu-Sensamide, radinyl	Oxigene, Roberts	phase II, III
metalloproteinase inhibitors	marimastat, AG-3340, CGS-27023A	British Biotech, Agouron, Novartis, Bayer	BBT in phase III
angiogenesis inhibitors	TNP-470, SU-5416, anti VEGF-mAb, thalidomide, DC101	TAP, Sugen, Genentech, Entremed, ImClone, etc	see angiogenesis project review for details

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Competitive Analysis

The project is on par with others in the industry. While second generation Abbott compounds are not yet in clinic, all of the compounds from other companies that are in clinical trials have deficiencies. While the Schering compound has the best oral PK profile, it is not particularly potent. The Janssen compound is potent, but has a poor PK profile. The Merck compound exhibited QTc prolongation and development has been stopped. The Bristol Myers Squibb compound, BMS-214662, which is in phase I, is an *in vitro* submicromolar inducer of apoptosis in human tumor cells and appears to be the most potent inducer of apoptosis of the known FTIs. This compound could have a different mechanism of action from the classical FTIs and have its own liabilities. LG42908 from LG Chemical is potent FTI and has good oral bioavailability (F= 91% in monkey), however; it's a CYP3A4 inhibitor and will have significant drug-drug interaction liabilities. Extensive preclinical pharmacology at Abbott has defined optimum parameters for a FTase inhibitor that may not be known to our competitors, or be achievable with the current generation of FTIs. Although not yet established, we anticipate that the Abbott compound will be improved over competitors' compounds with respect to potency, oral bioavailability, half-life, toxicity, efficacy, angiogenesis inhibition, and lack of resistance.

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# **DOPAMINE RECEPTOR AGONIST PROGRAM**

## **Descriptive Memorandum**

*February 2001*

**Abbott Laboratories**

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JH 008206**

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## D4 Agonists for Male Erectile Dysfunction

### Scientific Overview

Male erectile dysfunction (MED) is defined as the "inability to maintain an erection sufficient for satisfactory sexual intercourse" (NIH Consensus Panel) and results from physiological (organic), psychogenic causes, or a combination thereof. This disorder is associated with decreased quality of life, including personal well being, and diminished family and social relationships. In 1999, an estimated 77 million men over the age of 40 (52% of men over 40 years-old) in the seven major pharmaceutical markets experienced some degree of MED, and the prevalence increases with age. Approximately 10-20% of patients have severe or complete MED, and the majority of the population suffers from moderate disease. While the introduction of Viagra has increased the diagnosis rate of MED in the U.S., 75% or more of patients do not seek treatment. However, as the "baby boomer" generation ages, MED will become a more prominent concern and a growing number of patients are likely to seek treatment.

Abbott's male erectile dysfunction program targeting D4 dopamine receptors represents a novel therapeutic approach to the rapidly growing male erectile dysfunction (MED) market. The current gold standard for the treatment of MED, Viagra, acts peripherally at the penile smooth muscle level to induce erection by modulating the levels of cGMP. In contrast, a selective D4 dopamine agonist will act in the brain at the sites necessary for initiation of a successful erection. Targeting the D4 receptors in brain offers the potential for efficacy in patients with MED that do not respond to Viagra (for example patients with diabetes). Additionally, targeting D4 receptors should not result in any cardiovascular adverse events unlike Viagra which can cause serious cardiovascular effects in patients who are on nitroglycerine-based medications. Since safety is of paramount importance for any life-style disorder like MED, a new agent that does not have any contraindications or warnings related to safety issues may be positioned to become the gold-standard therapy.

Evidence for the potential of a selective D4 dopamine receptor agonist for the treatment of erectile dysfunction includes:

- The non-selective dopamine receptor agonist apomorphine (Uprima<sup>TM</sup>) has been shown to be effective in phase III clinical trials, and has received scientific approval for market in the EU, for the treatment of MED. This validates the utility of dopaminergic agonists to facilitate penile erections in humans. However, the clinical development of apomorphine for the US market has been hampered by dose limiting side-effects (emesis and syncope).
- Studies at Abbott have established that the efficacy of apomorphine (penile erection) and side-effect (emesis) are mediated by different dopamine receptor subtypes. There are 5 known dopamine receptors. Abbott scientists have discovered that the selective activation of D<sub>4</sub> receptors can facilitate penile erection in animals, while the D<sub>2</sub> receptor appears to mediate the emetic effect of apomorphine. The discovery of a D<sub>4</sub> selective agonist maximizes the possibility to identify a compound with equivalent/superior efficacy to apomorphine but devoid of its side-effect liabilities.

PPD is currently screening the Abbott library of compounds to identify novel and proprietary D4 dopamine receptor compounds. Initial hits have been identified that are as potent as any known D4 dopamine receptor agonist. The strategy is to aggressively profile these hits for selectivity across the five different dopamine receptor subtypes and to ensure that selective agents are effective in a number of preclinical in vivo models of MED and have no emetic or cardiovascular side effects. The D4 dopamine receptor agonist program will be discontinued if selective D4 agonists do not achieve at least a 30-fold separation between efficacy in a model of MED and cardiovascular/emetic side effects.

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Abbott has a competitive advantage in the race to exploit selective D4 dopamine receptor agonists for MED. A patent application covering the use of any selective D4 agonist for the treatment of MED has been filed and no other pharmaceutical company may have the range of preclinical models of efficacy and safety in addition to access to the clinical information gained from the development of apomorphine. Our molecular modeling group has facilitated advances in the design of selective D4 agonists.

### **Market Analysis**

The introduction of Viagra combined with increased disease awareness resulted in the MED market in the US exploding from \$157MM in 1997 to an estimated \$726MM in 2000. Worldwide, this market has seen similar growth, and is estimated at \$500MM for ex-US for 2000. Viagra currently dominates the MED market, with more than \$1billion in sales in the \$1.3 billion worldwide market in 1999, and >95% of the MED prescriptions in the US. The market growth is expected to continue, with an estimated CAGR in the US of 17.9% (2000 – 2005), fueled by increased awareness of MED, expanded use to wider patient segments for relationship or performance enhancement, and the introduction of heavily promoted new agents. Downward pressure on growth will come from continued perceptions of safety concerns, the limited efficacy of Viagra<sup>TM</sup>, and out-of-pocket cost to patients.

Market drivers influencing the potential of a D4 dopamine receptor agonist include:

- Patient Awareness and Demand Viagra has built considerable awareness of MED. However, in the US, only 10-25% of current MED patients seek treatment for this disorder. Ex-US the percentage of patients seeking treatment is lower (10%). This is mainly due to the lack of DTC promotional campaigns in the ex-US markets. Further market expansion requires continued patient and physician education.
- Product Safety: There are growing patient and regulatory concerns regarding the safety of Viagra. While, physicians currently perceive Viagra<sup>TM</sup> to be safe, if used by the correct patients, there is significant concern regarding the concomitant use of nitrates for cardiovascular disorders with Viagra. Approximately 10% of Viagra patient deaths have been attributed to use of nitrates. Thus, there is an opportunity to eliminate this concern for physicians and to expand the market.
- Product Efficacy: In clinical trials Viagra allowed successful intercourse in about 50% of attempts. The limited and inconsistent efficacy of the product has resulted in patient dissatisfaction and discontinuation, thus creating a chance to drive Viagra quitters or switchers, as well as new patients, to new, more effective, MED products. The demonstration of efficacy in a broader population of MED patients might also influence physicians to try an alternative product prior to Viagra. The delay in onset (~1hr) and the variability in onset of action from patient to patient is an additional complaint about Viagra. Product features of a selective D4 agonist such as a more rapid onset of action or more reproducible onset will have a positive influence on the market opportunity for MED therapies.
- Additional Indications: Use of a D4 dopamine receptor agon in other indications such as "relationship enhancement" (female sexual dysfunction and age-related decline in male sexual performance) offers an opportunity to both expand the potential market to include women and non-MED sufferers, and reduce the embarrassment of MED for patients. Additional research is required to identify meaningful endpoints in this expanded indication. Initial studies conducted by Pfizer showed that Viagra<sup>TM</sup> was not effective to treat female sexual dysfunction.

**Competitive Overview**

The following tables summarize the key competitive activities in regard to marketed products and products in the development pipeline. To date there are no reports any other company targeting selective D4 agonists for the treatment of MED, although a number of companies do have activities in the dopamine receptor arena for other indications that could be re-focused to MED if they became aware of Abbott's insights into the D4 receptor.

**A. Oral agents**

Approach	Compound/Product	Company(ies)	Status
PDE5 inhibition	Sildenafil (Viagra™)	Pfizer	Marketed
DA receptor	Apomorphine (Uprima™)	TAP	NDA filing withdrawn
Adrenergic	Phentolamine (Vasomax™)	Schering-Plough/Zonagen	NDA filing on hold (>1 year)
PDE5 inhibition	IC351 (Cialis™)	ICOS-Lilly	Phase III
PDE5 inhibition	Vardenafil	Bayer	Phase II-III

**B. Intranasal**

Approach	Compound/Product	Company(ies)	Status
DA receptor	Nasal apomorphine	Nastech	Phase II

**C. Intracavernosal agents**

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE <sub>1</sub> (Caverjet™, Edex™)	Pharmacia, Schwarz Pharma	Marketed
VIP receptor/ Adrenergic	VIP-phentolamine (Invicorp™)	Senetek	Marketed outside US
K channels	PNU 83757	Pharmacia	Phase II

**D. Intraurethral agents**

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE <sub>1</sub> (Muse™)	Vivus, Abbott	Marketed

**E. Topical**

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE <sub>1</sub> (Alprox-TD; Topiglan)	NexMed; MacroChem	Phase II and III

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MAR. 13. 2001 12:29PM

NO. 2199 P. 2/3

Brian J. Smith  
Assistant Secretary and Divisional Vice President  
Domestic Legal Operations  
Abbott Laboratories  
100 Abbott Park Road  
Abbott Park, Illinois 60064

March 13, 2001

John Hancock Life Insurance Company  
Investors Partner Life Insurance Company  
John Hancock Variable Life Insurance Company  
Attention: Stephen J. Blewitt  
John Hancock Place  
P.O. Box 111  
Boston, MA 02117

Ladies and Gentlemen,

I have acted as counsel for Abbott Laboratories, an Illinois corporation (the "Company"), in connection with the Company's collaboration with John Hancock Life Insurance Company, a Massachusetts corporation, Investors Partner Life Insurance Company, a Massachusetts corporation, John Hancock Variable Life Insurance Company, a Delaware corporation (collectively, "John Hancock") pursuant to the Research Funding Agreement made as of March 13, 2001 (the "Research Funding Agreement"). Capitalized terms used herein without definition have the meanings assigned to them in the Research Funding Agreement.

In connection with the opinions expressed herein, I have made such examination of matters of law and of fact as I considered appropriate or advisable for purposes hereof. As to matters of fact material to the opinions expressed herein, I have relied upon certificates and statements of government officials and of officers of the Company. I have also examined originals or copies of such corporate documents or records of the Company as I have considered appropriate for the opinions expressed herein. I have assumed for the purposes of this opinion the genuineness of all signatures (other than those of individuals signing on behalf of the Company which are genuine), the legal capacity of natural persons, the authenticity of the documents submitted to me as originals, the conformity to the original documents of all documents submitted to me as certified, facsimile or photostatic copies, and the authenticity of the originals of such copies.

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**JH 008210**

MAR. 13. 2001 12:29PM

NO. 2199 P. 3/3

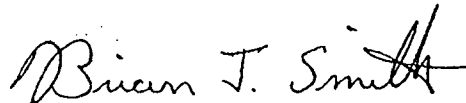
John Hancock Life Insurance Company  
Investors Partner Life Insurance Company  
John Hancock Variable Life Insurance Company  
March 13, 2001  
Page 2

Based upon the foregoing, and subject to the qualifications and limitations stated herein, I am of the opinion that: (i) the Company is duly organized, validly existing and in good standing in the State of Illinois; (ii) the Company has the requisite corporate power and authority to execute, deliver and perform the Research Funding Agreement; (iii) the Research Funding Agreement has been duly and validly authorized by the Company, and duly executed and delivered by an authorized officer of the Company and constitutes a valid and binding legal obligation of the Company enforceable against it in accordance with its terms; (iv) the performance of the Research Funding Agreement by the Company does not constitute a breach or violation of its organizational documents or any other agreement or understanding, written or oral, to which the Company is a party or any existing law, statute, rule or regulation by which the Company is bound; (v) no consents or approvals of any court or governmental authority is required on the part of the Company in connection with the execution, delivery, and performance of the Research Funding Agreement; (vi) there is no litigation pending, or to my knowledge threatened, which calls into question the validity of the Research Funding Agreement.

My opinion expressed above is limited to the law of the State of Illinois and the federal law of the United States, and I do not express any opinion herein concerning any other law.

The opinion set forth herein is rendered only to you and solely for your benefit in connection with the above described transactions. This opinion may not be relied upon by you for any other purpose, or relied upon by any other person for any purpose, without my prior written consent.

Very truly yours,







**FDA Contact Report**

Compound/Product Discussed: ABT-773 - End of Phase 2 Meeting

Application Type &amp; Number: IND 57,836

Date of Contact: November 27, 2000

	Name & Title	Group
FDA Person(s) Contacted	Jose Cintron, Sr. Project Mgr	Anti Infective Division
	Mercedes Albuerne, Medical Team Leader	"
	Nasim Moledina, Medical Officer	"
	Mamodikoe Makhene, Medical Officer	"
	Alma Davidson, Medical Officer	"
	Daphne Lin, Statistics Team Leader	"
	Erica Brittain, M.D., Statistics Reviewer	"
	Terry Peters, Pharm/Tox Reviewer	"
	Robert Osterberg, Pharm/Tox Team Leader	"
	Lilian Gavrilovich, Deputy Director	"
	Charles Bonapace, Biopharm Reviewer	"
	Frank Pelsor, Biopharm Team Leader	"
	Sousan Altaie, Micro Reviewer	"
	Jean Mulinde, Medical Officer	"
	Jim Timper, Chemistry Reviewer	"
	Charles Cooper, Medical Officer	"
	Albert Sheldon, Micro Team Leader	"
	Janice Soreth, Acting Division Director	"
	John Alexander, Medical Officer	"
	Diane Murphy, Office Director	Office of Drug Evaluation - IV
Abbott Representative(s)	Greg Bosco, Sr. Product Mgr	Regulatory Affairs
	Jeanne Fox, Director	Regulatory Affairs
	Jie Zhang, Statistician	Clinical Statistics
	Joaquin Valdes, Physician	Anti Infective Venture
	Carol Meyer, Operations Manager	Anti Infective Venture
	Bob Flamm, Microbiologist	Microbiology
	Linda Gustavson, Pharmacokineticist	Clinical Pharmacokinetics
	David Morris, Statistician	Clinical Statistics
	Maria Paris, Physician	Anti Infective Venture
	George Aynilian, Associate Venture Head	Anti Infective Venture
	Carl Craft, Venture Head	Anti Infective Venture
	John Leonard, Vice President	Research & Development
	Reid Patterson, Vice President	Drug Safety

**Subject of Meeting:**

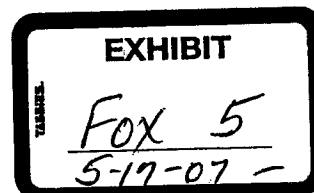
The purpose of the meeting was to introduce the oral tablet Phase 3 development plan, discuss potential issues, and address any questions regarding the plan or Phase 2 study results.

**Report of Meeting:**

The meeting began with introductions from both sides. As Carl began his presentation, Dr. Soreth stated that in case there was some misconception regarding the result of the telecon held on 11/20/00, she wanted to say that the ABT-773 program was at this point not on clinical hold.

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ABBT205257



Carl began his presentation with a slide showing the proposed indications and treatment durations we were planning to file in the NDA. He showed a series of slides which summarized all the Phase 3 studies we are planning; those starting in 2000 and those slated for 2001. This was the first time FDA saw the proposed dose-selection studies for pneumonia (CAP) and sinusitis (ABS). Dr. Brittain had a few questions regarding the objectives of the studies and the proposed interim analyses, but stated that she would be faxing us all of her comments in more detail. Carl stated that the objectives of the studies were: to pick a dose for the large, well-controlled, comparative, pivotal studies to be conducted in 2001, and to meet the specific pathogen criteria as required for the second supportive trials in the FDA guidance for CAP and ABS. There was lengthy discussion around these study designs. It was stressed to FDA that we still intend to conduct a large, well-controlled, double-blind, comparative trial for each of these indications. FDA advised us there might be a problem using Augmentin 875 mg BID for the sinusitis trial. They would prefer us to use 500 mg TID. Carl committed that we would provide the results from these two trials to FDA for review.

The next slide shown detailed our intention to request a claim for macrolide and penicillin resistant bacteria and atypical bacteria, and the supporting data we proposed to provide to support these claims. Dr. Albuerno stated that we could pool isolates for CAP and ABECB but not for ABS (we proposed pooling from all three). Dr. Soreth stated that there is currently no guidance document available addressing specific requirements for resistant claims but mentioned that there is data from other products (e.g. levofloxacin) that is available in the public domain. As far as our proposal for number of isolates, numbers >10 would be acceptable with good data for susceptible pathogens, but there has been an instance (with linezolid) where <10 was not approvable, but in that case only one or two patients had bacteremia and responded well to therapy. It was stated that a number of bacteremic patients would be required in order to adequately evaluate clinical success against penicillin resistant *Strep pneumoniae*. The comment was made that with oral therapy alone we would probably be hard pressed to find enough patients with bacteremia, that oral/IV therapy gave us a better chance. Dr. Soreth stated that FDA has not seen data supporting "macrolide resistant *Strep pneumoniae*" as a clinical concern. They also said that there is no good body of evidence supporting macrolide resistant *Strep pyogenes* either.

The next topic discussed was the ECG monitoring plan regarding the six Phase 3 studies starting in 2000. We proposed that ECG's would be performed in 5/6 of the studies. In total, we would be gathering ECG data on ~2000 subjects exposed to ABT-773. ECG's will be performed pre-, during, and post-therapy. Additionally, the timing of the ECG and the timing of the dose before the ECG will be documented. FDA requested that we amend all informed consents to mention possible effects on cardiac repolarization caused by ABT-773. Various examples of wording was then discussed and we agreed that we would amend the informed consents for all IND studies. Dr. Soreth asked why we were not doing ECG's in the sixth study. Carl stated that the European pharyngitis study would not include ECG's based on recommendations of our European advisors based on the number of existing visits and the likelihood of subject reluctance to participate in a trial for this disease with so many visits. FDA strongly disagreed with this justification. Dr. Murphy expressed concern that we were blatantly misinforming the subjects in that trial by not including a procedure that would monitor a potentially serious adverse event that was being included in all other studies. This issue was left unresolved. Other comments regarding the collection of a blood sample taken at the on-therapy ECG, etc. were made. All issues were addressed in a subsequent written correspondence by FDA (faxed 12/5/00, Abbott response 12/14/00).

Relating to the topic of possible adverse effects on cardiac repolarization, the results of the previously submitted toxicology studies were discussed. Dr. Peters requested additional data in the dog model. The requested study should be a two-week acute study with telemetry and the study can run concurrent with the Phase 3 clinical trials. At this point Reid offered to provide some background information. He indicated that the emetic activity of ABT-773 in the unanesthetized dog limits exposure in this species, leading to our selection of the cynomolgus monkey as the non-rodent model. While the primate did not indicate a risk for QTc prolongation, exposures of 17 times the human C<sub>max</sub> in anesthetized dogs did lead to some prolongation. Owing to differences in protein binding, the dog receives about 3 times the amount of unbound drug than does the human with identical exposures, perhaps expanding our margin of safety. Various proposals for the study were discussed between Reid and Drs. Peters and Osterberg. We committed to sending draft protocols to Dr. Peters for review.

Carl briefly discussed the Phase 2 ECG data. Dr. Soreth informed us that they have begun to ask for special population studies with drugs that show an effect on ECG's. In this case they would be looking at a study in otherwise healthy subjects with underlying cardiovascular disease. She commented that only looking at the effects

of ABT-773 in comparator trials might not be realistic (i.e., cisapride and terfenadine looked safe in the clinic too). Dr. Murphy commented that it is in both of our best interests to get all the information we can to show how to use the drug safely.

The rest of the meeting was spent answering specific questions regarding the four main Phase 3 trials (CAP, ABS, ABECB & pharyngitis). Most of the comments related to minor protocol changes. All of the issues discussed were subsequently provided to Abbott by fax on 12/5/00. Abbott formally responded to the fax in IND 57,836, Serial No. 066, dated 12/14/00.

Action Items:

- Amend Phase 3 informed consents to incorporate statements relating to: possible effects on cardiac repolarization caused by ABT-773, possible interactions with other drugs, and stronger precautions for women of childbearing potential.
- Provide full narratives from Phase 2 studies of all patients who had an adverse event of syncope or elevated liver enzymes.
- Submit draft toxicology protocol(s) for comment prior to initiating the studies.
- Submit results from CAP and ABS dose-selection trials when available.
- Submit draft protocols for the two well-controlled, comparative, pivotal studies for CAP and ABS (to be conducted in 2001) for comment as soon as available.



## ASCO 2001 MMPI Update

- Ten MMPI abstracts were presented
- Prinomastat, marimastat & Bay 12-9566 reported negative findings
- Possible reasons
  - Under dosing due to dose limiting toxicity (joint toxicity)
  - Inappropriate tumor selection
  - Inappropriate tumor stage (late vs. early)
  - Phase II development not done for prinomastat & Bay 12-9566
- BMS 275291 did not show joint toxicity in Phase I. Phase II studies are being initiated in NSCLC & Kaposi's sarcoma

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FOR ID *4* *26-07* *1995*

## Prinomastat

- Non-small cell lung cancer
  - Combination with paclitaxel & carboplatin
  - No survival benefit
- Hormone refractory prostate cancer
  - Combination with mitoxantrone & prednisone
  - No effects on: PSA, progression free survival, overall survival
- Refractory metastatic breast cancer
  - Phase I/II single agent (n = 44)
- Grade 2 joint toxicity in above trials at all dose levels (5,10,25 mg bid)
- Studies in earlier stage tumors are still ongoing

## Marimastat

- Small cell lung cancer
  - Following response to 1<sup>st</sup> line therapy
  - 10mg vs. placebo
  - Total 155 patients
  - No benefit on progression free survival or overall survival
- Glioblastoma
  - Post surgery & radiotherapy
  - 10mg vs. placebo
  - Total 162 patients
- High dropout rate due to joint toxicity



## Bay 12-9566

- Ovarian cancer (stage III or IV)
  - 800mg bid vs. placebo
  - Study was discontinued prior to full enrollment due to lack of activity in pancreatic cancer and SCLC
  - No benefit on survival

## BMS 275291

- Phase I studies
  - Healthy volunteers (n = 40 males)
  - Cancer patients (n = 44)
- No joint toxicities (possibly due to lack of sheddase activity)
- No MTD through 2400mg / day
- Phase II plan
  - Non small cell lung cancer in combination with paclitaxel & carboplatin
  - Kaposi's sarcoma
  - Dose 1200 mg / day

# ABT-518 Phase I Multiple-Dose Study in Cancer Patients M00-235

- Patients enrolled to date
  - 25 mg / day 4
  - 50 mg / day  $\frac{3}{7}$
- Dosing duration up to 57 days
- Patients will continue dosing until disease progression or adverse events
- No musculoskeletal effects reported to date
- Next dose is 100 mg / day

# ABT-518 Development Recommendations

- Continue the ongoing Phase I study

## Objectives

- Determine target dose required to achieve target plasma concentration of 1-3  $\lambda$ M
- Assess safety following chronic administration
- Stop development if Grade 3 or 4 toxicities are attributed to doses at or below target dose
- Stop for joint toxicity
- If target dose is well tolerated, initiate a pharmacodynamic/proof of principle study with external funds (e.g., NCI-CRADA) and/or outlicense
  - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity



# January 2001

## ABT-773 Project Status Report

### Monthly Highlights

- We sent responses to the FDA based on their written comments from the end of Phase II meeting on Dec 14<sup>th</sup> and have only received feedback on the CAP protocol. We have implemented all requested changes for the other 3 indications and have IRB approved amendments. We have also re-submitted to European ethics committees and MOHs were required.
- All Phase III U.S. studies are actively enrolling patients. European studies will start enrollment this month, as we have initial approvals in at least one country for each protocol.
- Plans are in place to initiate sites in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in June. This will enable us to continue enrolling once the season in the Northern Hemisphere comes to a close and will help to insure that we obtain sufficient patients to make a dose selection for these 2 indications.
- A decision on funding for the IV formulation is required in February to initiate the first Phase I study by April 2<sup>nd</sup>. This study will enable us to determine the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go by September is critical if we would like to have an IV filling within a year of the tablet filling.
- The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period.

<b>Key Progress Gauges - January Accomplishments</b>		<b>Target Date</b>	<b>Status</b>
Complete End of Phase II CMC/BioPharm package to request meeting with FDA.		01/31	To be completed by 2/16
Complete Phase III protocol amendments and re-submit to European Ethics committees.		01/31	Complete
Complete manufacture of final NDA formulation lots.		01/31	Complete
Make a pediatric strategy recommendation based on team review of pediatric data from formulation, PK, taste evaluations.		01/31	Strategy meeting scheduled for 2/16.
Complete pilot scale activities in IDC for the U.K. manufacturing site.		01/31	Complete
<b>February Projections</b>		<b>Target Date</b>	<b>Status</b>
Initiate enrollment in European Phase III studies.		02/19	
Initiate commercial scale process development for the US formulation.		02/12	
Deliver bulk drug campaigns 14 and 15.		02/16	
Initiate NDA stability of final NDA formulation lots.		02/06	
Submit Phase III comparative CAP & ABS protocols for CRO bids to initiate these studies in 4 <sup>th</sup> Q 2001.		02/28	
Finalize BAL protocol for Japan to initiate in April.		02/28	

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**January 2001**  
**ABT-773 Project Status Report**

**Key Issues/Decisions/Events**

Area	Issue/Decision/Event	Progress
SPD/PARD	A change in bulk drug physical or chemical properties during formulation development will result in a delay in the Aug 2002 filing date. If at the 1200L scale, a delay of up to 18 months.	A strategy for the bulk drug lots that will be used in the NDA formulation runs will be reviewed with the CMC Technical Committee in early December. Bulk drug properties and granulation variables are being evaluated as a means to develop appropriate physical specifications for the bulk drug.
Regulatory	An end of Phase II meeting with FDA was targeted for the end of September/mid October timeframe, but rescheduled to the end of November at the request of FDA.	Meeting with FDA was held on November 27 <sup>th</sup> . QT effects are the current hot topic for the FDA, and was reflected in the changes they requested to the Phase III program. They also requested an acute tox study in dog to further evaluate cardiac effects. The required "body of evidence" for obtaining a resistance claim for <i>s.pneumo</i> was discussed and the FDA recommendation included having an IV formulation to get bacteremic patients and more serious CAP infections. <b>Protocol amendments have been signed off incorporating all FDA requested changes and implemented in the U.S. and Europe.</b>
Regulatory	Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects.	FDA concern is whether ketolides behave like macrolides and whether there may be a class effect. They also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. ECG monitoring will be done in all Phase III studies with the exception of the ASP study in Europe.
SPD	Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch.	The End of Phase II CMC meeting with FDA will be requested for January 2001 to present the package on starting material definition for step 5 intermediate. Meeting is targeted for the end of March.
Venture/NPD	The pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged.	Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Phase IIIa studies to be complete by 5/2001 to decide the dose requirements for CAP and ABS. <b>To address this issue and potentially create a new model for evaluating PK/PD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts June-July 2001 to define further study.</b>
NPD	Phase IIIa data will be important predictors of commercial value of compound (QD vs BID dosing for CAP/Sinusitis, efficacy, adverse event rates.	Phase IIIa studies to be complete 5/2001. FDA changes to the Phase III protocols creates a challenge for us to still meet the Go/No Go decision for the QD vs BID dose for CAP and ABS by June. The team is working to overcome the challenges as much as possible.

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**January 2001**  
**ABT-773 Project Status Report**

Area	Issue/Decision/Event	Progress
<b>Venture</b>	Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> .	FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required, CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim.
<b>Clinical</b>	The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time.	FDA requested changes are being assessed for protocol amendments. The subject Informed Consent revisions were submitted to central IRBs and approval was obtained by Dec. 8 <sup>th</sup> . <b>No FDA feedback was received on our responses to the End of Phase II meeting for ABS, ABECB or ASP protocols. We have incorporated all requested changes and submitted to IRBs in the U.S. and Ethics Committees/MOHs in Europe. European study enrollments expected to start in mid-February. We are working to start countries in the So Hemisphere to compensate for the delays.</b>
<b>Japan</b>	Due to the dose change in the base development program, Phase I will be repeated in Japan to further evaluate dose-ranging. An increase in liver enzymes was observed in the low and medium dose groups of Japanese volunteers in the first study in Hawaii, and will be further evaluated in the Phase I studies done in Japan. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan.	<b>The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period. The Japanese BAL study will start in April. Dose selection and BAL results need to be available prior to a meeting with Kiko to discuss the Phase II/III strategy.</b>
<b>HPD</b>	The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Year 2001 funding was committed by HPD.	HPD funding for 2001 (\$7MM) is no longer approved. At the ABT-773 Portfolio meeting, Jeff Leiden committed to find funding (approx. \$1MM) to do the Phase I studies for the IV in 2001 to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. <b>Need confirmation on funding availability in February to initiate Phase I in April.</b>

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**January 2001**  
**ABT-773 Project Status Report**

Project Cost Summary - January					
\$000's Activity	Cumulative through 2000	YTD Actual	Projected Year-end	Current Funded Year-end	Variance
Clinical Program	46.5	6.6	61.7	61.7	...
CMC (PAR, SPD & IDC)	77.9	1.4	21.7	21.7	...
Drug Safety	9.0	.1	1.9	1.9	...
Other Support Costs	20.4	.3	2.7	2.7	...
Total	153.8	8.4	88.0	88.0	...
					287.7 *

**Tablet NDA = 8/2002; IV Formulation unfunded; Pediatric Formulation unfunded .**

\* Cumulative cost to NDA based on 3Q 2002 filing.

Clinical Study Progress						
Protocol # - Study Name	Start (1st Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients	Current Enrollment	
M99-048, Phase II Dose Ranging, ABECB	9/1/99	3/31/00	3,885	300	384	
M99-053, Phase II Dose Ranging, Sinusitis	9/1/99	4/30/00	3,172	300	292	
M99-054, Phase II Dose Ranging CAP	9/1/99	4/30/00	4,089	300	187	
M00-219 Phase III CAP, Dose Ranging	11/7/00	4/30/01	14,400	800	68	
M00-216 Phase III ABECB vs Azithromycin	11/7/00	4/30/01	7,381	600	125	
M00-217 Phase III ABECB vs Levofloxacin	11/7/00	4/30/01	4,600	500	0	
M00-225 Phase III Sinusitis Dose Ranging	11/7/00	4/30/01	7,200	600	126	
M00-223 Phase III Pharyngitis vs Penicillin 250mg TID	11/7/00	4/30/01	4,340	520	161	
M00-222 Phase III Pharyngitis vs Penicillin 500mg TID	11/7/00	4/30/01	5,000	520	0	

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# January 2001

## ABT-773 Project Status Report

### Business Rationale

Date: January 2001

Acquired

Franchise: Anti-infective

Venture: Anti-infective

ABT #:

ABT-773

Trade & Generic Name: TBD, TBD

Mechanism of Action: Ketolide, antimicrobial

Indications: Acute Exacerbations of Chronic Bronchitis, Community

Pneumonia, Pharyngitis, Acute Maxillary Sinusitis

### Product Profile

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Activity against Gram +, Gram -, atypicals	3/1997	High	Confirmed	High
Activity against <i>H. influenzae</i> = azi	3/1997	High	Confirmed	High
Active against 80% of Gram + resistant strains of efflux and MLS-c	3/1997	High	Confirmed	High
Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel	3/1997	High	Confirmed	High
Incidence of GI side effects=azi	3/1997	Low	Not Met	High
Incidence of drug-interactions = clari, no contraindications	3/1997	High	6/2001	Medium
QD dosing adult/tablet	3/1997	Medium	6/2001	High
QD dosing ped OS	3/1997	Medium	9/2000	Medium
QD dosing for IV	3/1997	Medium	12/2000	High
Comparable pain at injection site than azi	3/1997	Medium	12/2000	Low
Less metallic taste than clari XL	3/1997	Medium	6/2001	High
OS equal in taste to Azi, Omnicef		Low	9/2000	High
5-day therapy for most indications	3/1997	Low	6/2000	High
COGS > 80% SMM at launch	3/1997	High	12/2001	Low
Maintain balanced plasma/tissue levels similar to clari		Medium	12/2001	Medium

- Probability Key:  
High = 70-100%  
Medium = 30-69%  
Low = 0-29%

### Market Forecast

	PPCC/DDC 3/1997	Revised 1/1999	Current Revised 8/2000 Tab/Cap Only*
Patent Status:	9/2016	9/2016	9/2016
NDA Filing:	12/2000(tab/cap)	8/2002 (all)	8/2002 (tab/cap)
	9/2001(OS, IV)		
Ex-U.S. Filings:	2/2000(tab/cap)	8/2002 (all)	8/2002 (all)
	9/2001(OS, IV)		
Projected U.S. Launch:	4/2002(tab/cap)	9/2003	8/2003
	1/2003(OS, IV)		
Projected ex-U.S. Launches:	4/2002(tab/cap)	9/2003	8/2003
	1/2003(OS, IV)		
Peak TRx Share, U.S.:	4.4%TC;4.7%OS; 3.3%IV	4%TC;4%OS; 10%IV	7.5%
	N/A		
Peak TRx Share, ex-U.S.:	N/A	3.3%TC;N/A OS, IV	4.4 to 6.9%
Peak Sales, U.S.:	\$428TC; \$118OS	\$399TC; \$58OS	\$432
(\$MM)	\$26IV	\$13.8IV	
Peak Sales, ex-U.S.:	N/A	\$360TC;N/A OS, IV	\$386
(\$MM)			
Post-Tax NPV @ 12.5%, U.S.:	N/A	\$200TC; (\$6.1)OS	\$297
(\$MM)		(\$1.1)IV	
(no clari cannibalization)		(note: discount rate was 15%)	
Post-Tax NPV @ 12.5%, ex-U.S.:	N/A	\$240TC; N/A OS, IV	\$208
(\$MM)		(note: discount rate was 15%)	
(no clari cannibalization)			
Avg daily dose			150mg QD
Target Drug Cost/kg at Launch	\$1163TC; \$2173OS	\$3633TC; \$291OS	\$3000
	\$3720IV	\$8953IV	
SMM at Launch (U.S., Ex-U.S.)		86%TC;63%OS;100%	85%, 87%
SMM at Year 5 (U.S., Ex-U.S.)		IV94%TC;82%OS;58%I	90% 93%

\* Includes Tab/Cap only. A development plan will be established for OS and IV programs.

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# January 2001

## ABT-773 Project Status Report

### Project Overview

Metrics Dates	
Description	Date
DDC Meeting	3/1997
Start of first GLP animal tox study	6/1997
First dose in human (beg. Phase I)	12/1997
First dose in patient (beg. Phase II)	9/1999
First dose in Phase III	11/2000
Last Patient/Last Visit	4/2002
NDA Filing	8/2002
NDA Approval	8/2003
Europe (EMEA) Filing	8/2002
Europe (EMEA) Approval	8/2003
Japan Filing	TBD
Japan Approval	TBD

See the following page for a summary of Bulk Drug deliveries in SPD.

### PARD

Activity	Plan 12/1998	Actual
Phase I Formulation (Caps)*	12/1997	12/1997
Phase II Formulation (Tablet)	7/1999	8/1999
Clinical Supplies Phase IIB	7/1999	8/1999
Phase III Formulation (Tablet)	4/2000	7/2000
Phase III Clinical Supplies Manufactured	9/2000	9/2000
NDA Lots (3) Completed	7/2000	01/2001
Completion of 1 Year Stability for NDA	8/2001	
Formulation Peer Review	11/2001	

### Toxicology

Toxicology Activity	Plan Start 12/1998	Actual Start Date	Report Completed
2-week oral Rat/Monkey	7/1997	6/1997	9/1998
Acute Studies	8/1997	8/1997	12/1997
Mouse Lymphoma/Micronucleus	11/1997	11/1997	4/1998
1 Month Rat/Monkey	12/1997	12/1997	12/1998
Pregnant Rat/Rabbit RF	1/1998	1/1998	11/1998
SEG II Rat/Rabbit	3/1998	3/1998	2/1999
Guinea pig sensitization	11/1998	11/1998	2/1999
3 Month oral Rat/Monkey	9/1999	10/8/1999	8/2000
Seg I/III Rat	9/1999	10/8/1999	12/2000
IV Irritation studies, set 1	7/1999	7/15/1999	8/1999
IV Irritation studies, set 2	2/2000	2/2000	3/2000
IV 2-week Rat/Monkey Studies	6/2000	6/2000	01/2001
Neonatal/Juvenile Rat	10/1999	11/1999	7/2000

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January 2001  
ABT-773 Project Status Report

**SPD ABT-773 Bulk Drug Deliveries Update**

	<u>Target Date</u>	<u>Amount</u>	<u>Delivery Date</u>	<u>Amount</u>	<u>Lot #</u>	<u>Amount after milling</u>
Campaign 1	2/28/99	200 Kg	2/23/99	209 Kg	50-007-CA-00	207.5 Kg (2/26)*
Campaign 2a	6/15/99	140 Kg	6/17/99	131 Kg	54-702-NI-00	129.4 Kg (6/19)*
Campaign 2b	7/15/99	140 Kg	7/21/99	121.5 Kg	55-208-CB-00	119.3 Kg (8/4)*
Tox lot	8/30/99	5 Kg	8/25/99	6.1 Kg	55-718-NI-00	
Campaign 3a	9/30/99	160 Kg	10/8/99	170.5 Kg	58493CB00	138.4 Kg (10/16)*
Campaign 3b	10/21/99	160 Kg	10/11/99	176.5 Kg	58494CB00	169.5 Kg (10/16)*
Pilot run 1	-----	15 Kg	10/30/99	18.9 Kg	59763N100	no milling
Pilot run 2	-----	15 Kg	2/5/00	15.5 Kg	61790NI00	no milling
Pilot run 3	-----	25 Kg	1/30/00	27.5 Kg	62764CB00	27.3 Kg (4/18)*
Campaign 4	12/10/99	320 Kg	11/23/99	355 Kg	61741CB00	309 Kg (3/2)*
Campaign 5	12/30/99	300 kg	12/16/99	300.5 Kg	60665CB00	269.2 Kg (3/3)*
Campaign 6	2/28/00	280 Kg	2/23/00	321 Kg	62796CB00	315.5Kg (3/6)*
Campaign 6 (IV)	2/28/00	15 Kg	2/22/00	20 Kg	62797CB00	18 Kg (3/15)*
Campaign 7	3/30/00	300 Kg	4/10/00	370 Kg	63890CB00	361.2 Kg (4/18)*
Campaign 7 (IV)	3/30/00	5 Kg	3/29/00	19 Kg	63889CB00	17.2 Kg (4/11)*
Campaign 8	4/25/00	200 Kg	5/11/00	263 Kg	64970CB00	256.5 Kg (5/15)
Campaign 8 (IV)	4/25/00	15 Kg	4/25/00	19.8Kg	64971CB00	17.7 Kg (5/11)*
Campaign 9	6/15/00	300 Kg	6/14/00	375.7 Kg	65064CB00	355.7 Kg (6/20/00)
Campaign 9 (IV)	6/15/00	15 Kg	6/5/00	18.1Kg	65065CB00	16.7 Kg (6/9/00)*
Campaign 10	7/15/00	300 Kg	7/26/00	361.2 Kg	67176CB00	359.0 Kg (8/10/00)
Campaign 11	8/15/00	300 Kg	8/4/00	333.7 Kg	68285CB00	271.9 Kg (9/7/00)
Campaign 12	10/6/00	300 Kg	9/27/00	356 Kg	69458CB00	292.3 Kg (12/8/00)
Campaign 13	11/23/00	300 Kg	11/15/00	351.2 Kg	71665CB00	349.1 Kg (12/20/00)
					Total (year 2000)	2,815.5 Kg

\* Weight after rework

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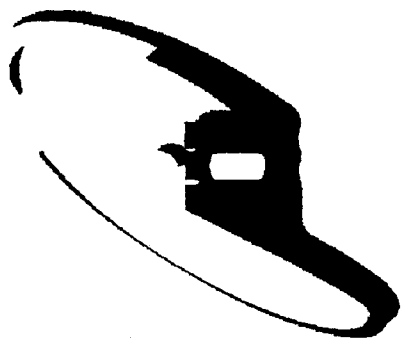
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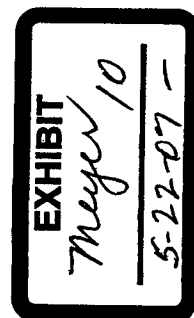
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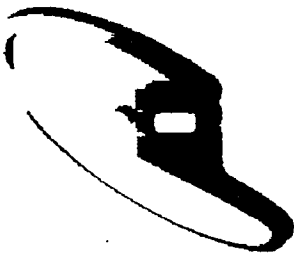
# ABT-773 Update February 12, 2001





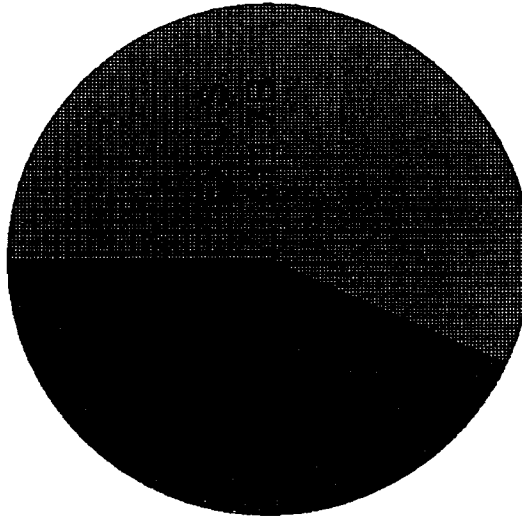
# Agenda

- Introduction
- The molecule
- Phase III tablet program Issues
  - QT
  - Liver Function
  - Dosing
- IV program
- Pediatric program
- Japan program

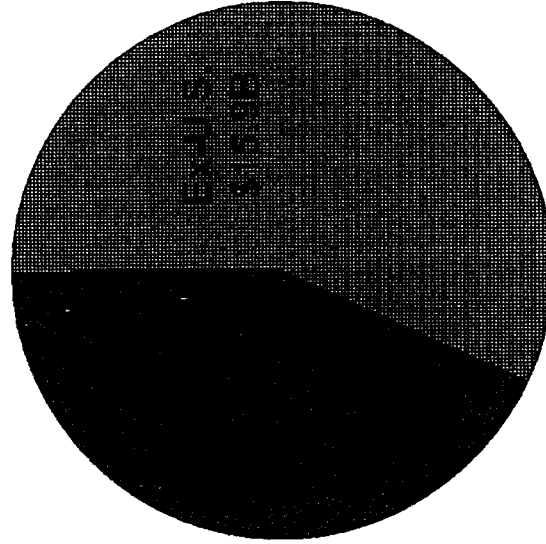


## Global Antibiotic Market Sales Current vs Future Projection

1999 Global Sales \$20.6B



2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis



# Global Market Drivers

## Negative vs Positive Drivers

### • Antibiotic Resistance

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓  
Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

### • Patent Expirations

May increase price sensitivity and bargaining power of MCOs ↓  
Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

### • Unmet Need ↓

—Overall unmet need relatively low  
—Cost, convenience, tolerability take on added importance  
—Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

### • Competition ↓

—6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox  
—Continued discovery/development activity by key competitors  
—High level of promotional activity

Negative driver ↓

Positive driver ↑

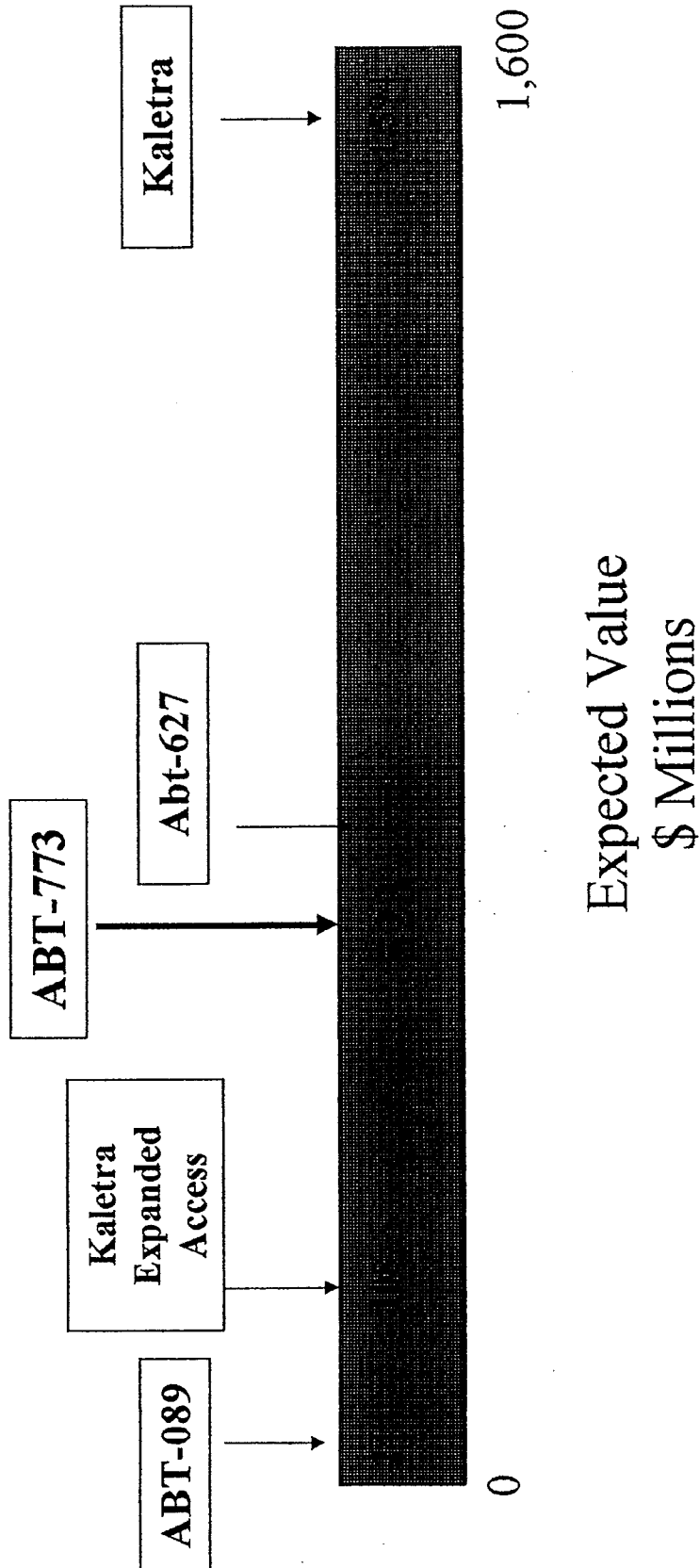
# Key Success Factors

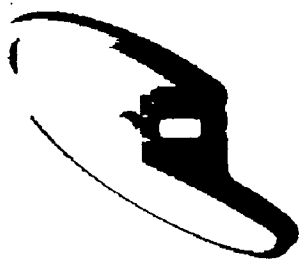
## U.S. vs ex-U.S.

U.S. Assessment			Ex-U.S. Assessment	
Profile	Efficacy	++	Requires a certain baseline level of efficacy across all indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy	+++ While also difficult to differentiate based on efficacy, efficacy takes on added importance with respect to regulatory approval, especially in CAP.
	Tolerability	+++	Success of Zithromax and Levaquin have redefined expectations for tolerability of new agents; agents must offer very good tolerability given numerous alternatives	++ Although important, markets are willing to bear somewhat higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE hurdles will continue to be increased
	Convenience	+++	Zithromax and recent quinolones have moved the market toward short course therapies dosed once daily; Biaxin in 1991 represented the last major BID entrant	++ While in some cases durations are even shorter (azi 3-day AECB), market levies relatively minor penalties for BID dosing
	Resistance Claim	++	Important to leverage the overall ketolide message, and to maximize formulary access, although availability of data may be able to accomplish same end	+++ May prove critical in the regulatory decision of approvability, as well as in setting premium pricing
	Price	+	Able to set price in accordance with optimal price/demand relationship; only moderate price sensitivity in market, though this could increase with increased number of generic competitors over mid-term	+++ Pricing figures heavily into the overall profitability of the compound and is governed by merits of product profile relative to other agents.
Regulatory	Approvability	+	With data showing equivalence to comparators, is not a major area of concern	+++ Will take into consideration PK profile in addition to clinical data, which could weaken argument for approval; given the pivotal nature of CAP approval to overall compound viability, regulatory risk is magnified; will require very strong clinical data if 150-mg OD is to be supported
Profitability	COGS	+	Allows for > 90% SMM given price parity to Zithromax	++ Due to pricing constraints, COGS represents a larger issue; current estimates are 76% SMM at launch rising to 87% peak
	Price	+	Assumes price parity to Zithromax	+++ Profile may limit optimal pricing

+ Minor Factor  
 ++ Moderate Factor  
 +++ Major Factor

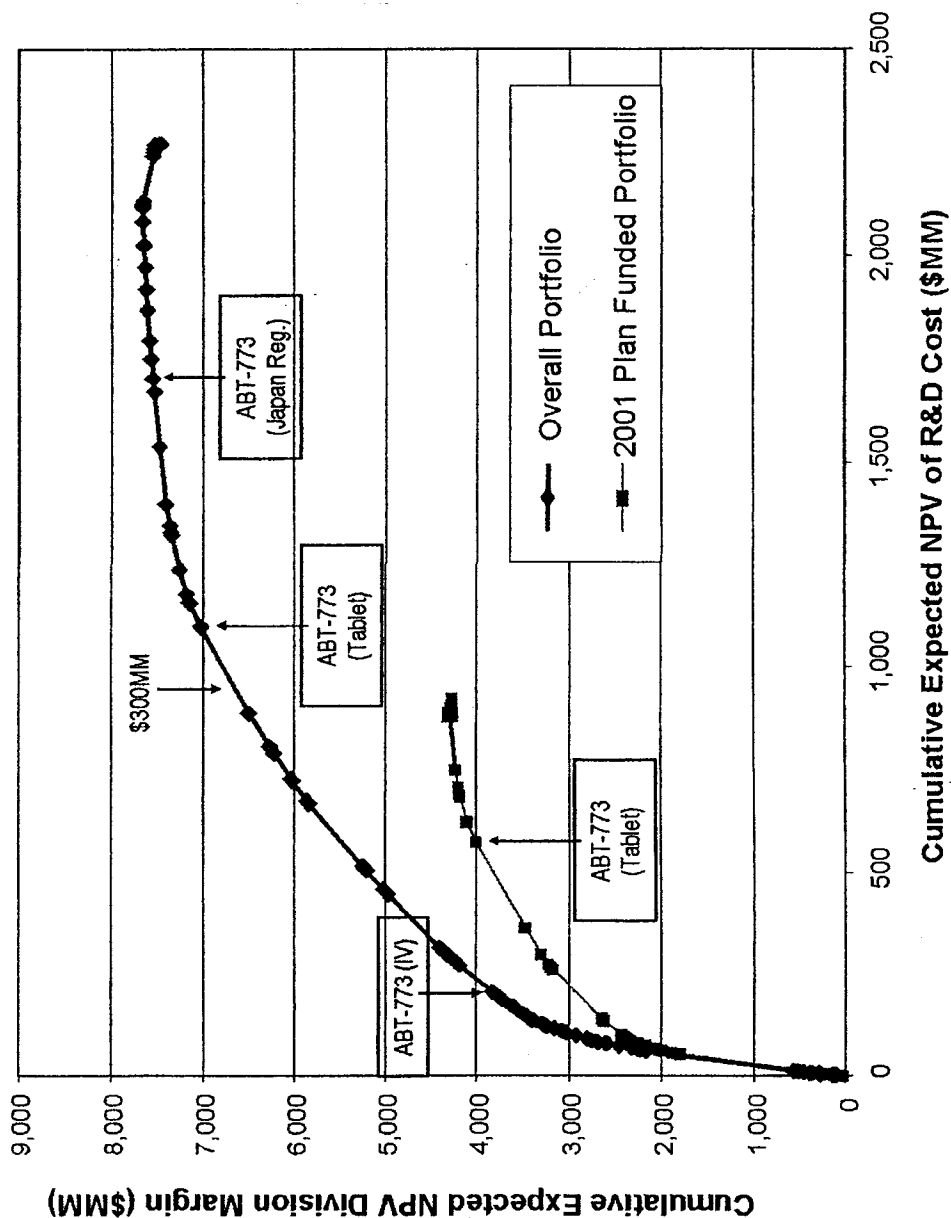
# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***

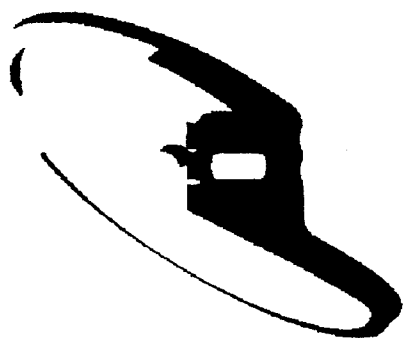




# ***ABT-773 Comparison with other funded projects in 2001 Plan Portfolio***

## **Portfolio Productivity Analysis**

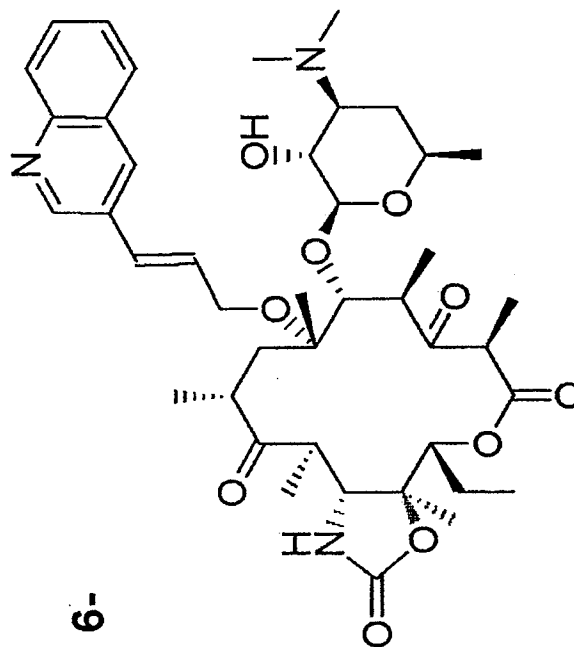




**ABT-773**

**The Molecule**

# ABT-773 Ketolide

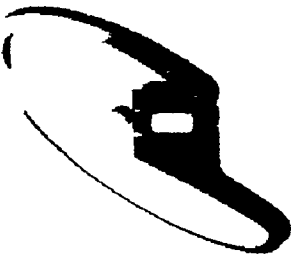


•Quinolylallyl propenyl moiety at the 6-  
0 -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position

ABT-773



## ABT-773 Ketolide

- **Ketolides are a Novel Class of Antimicrobial**
  - Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development

# Microbiology

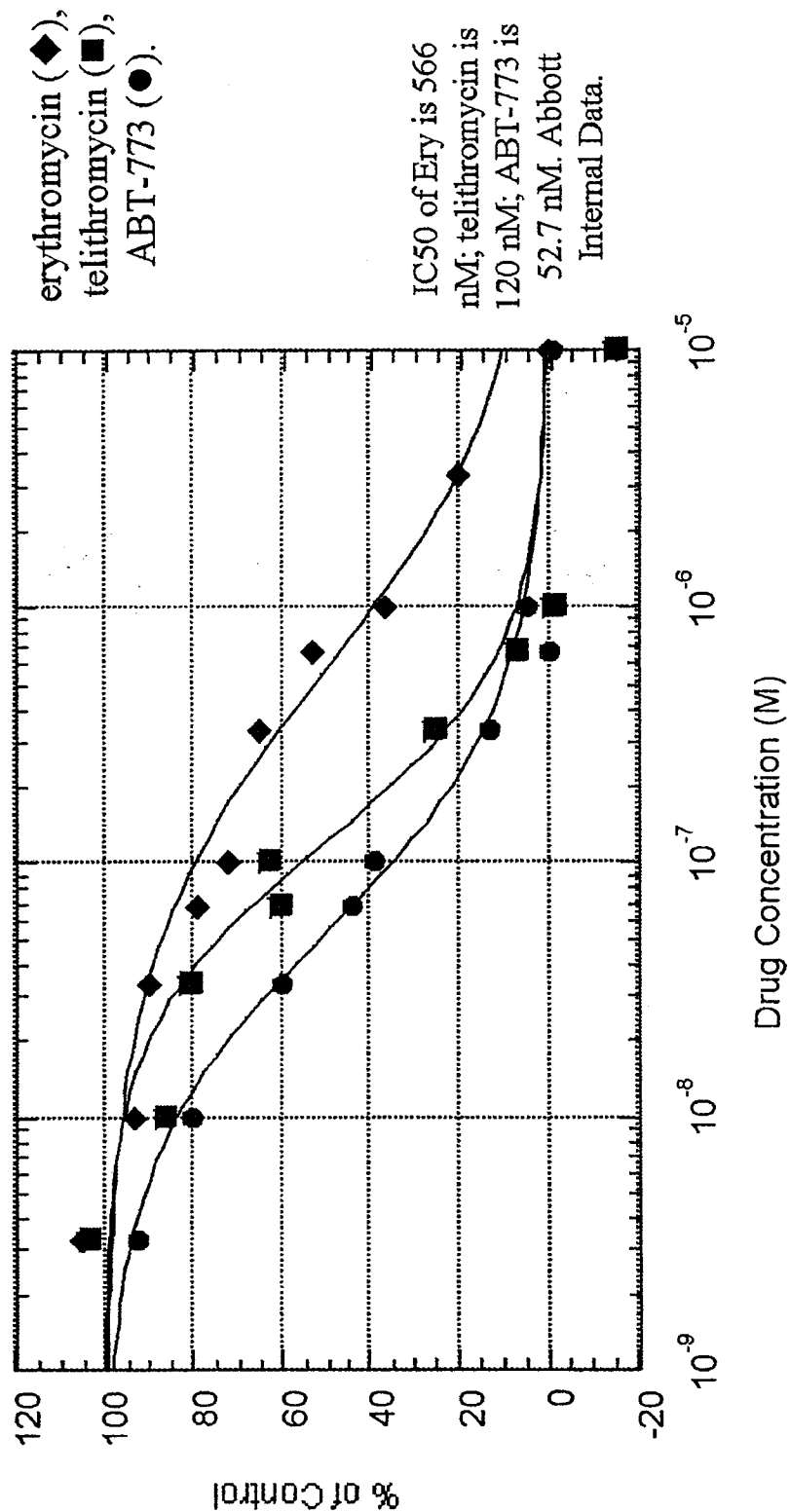
MIC<sub>90</sub>  $\lambda$ g/ml

Organism	ABT-773	Ketek	Clari	Azi
<i>S. pneumoniae</i> ery-S	0.008	0.004	0.03	0.12
<i>S. pneumoniae</i> mef	0.12	1.0	4.0	16.0
<i>S. pneumoniae</i> erm	0.01	0.12	>32	>32
<i>S. pyogenes</i> ery-S	0.12	2.0	1.0	2.0
<i>S. pyogenes</i> ery-R	0.5	>8.0	>32	>32
<i>M. catarrhalis</i>	0.25	0.25	0.5	0.25
<i>H. Influenzae</i>	2.0	2.0	16	2.0
Legionella	2.0	2.0	0.06	1.0
<i>M. Pneumoniae</i>	<0.005	<0.005	0.008	<0.005
<i>C. Pneumoniae</i>	0.015	0.06	0.06	0.12



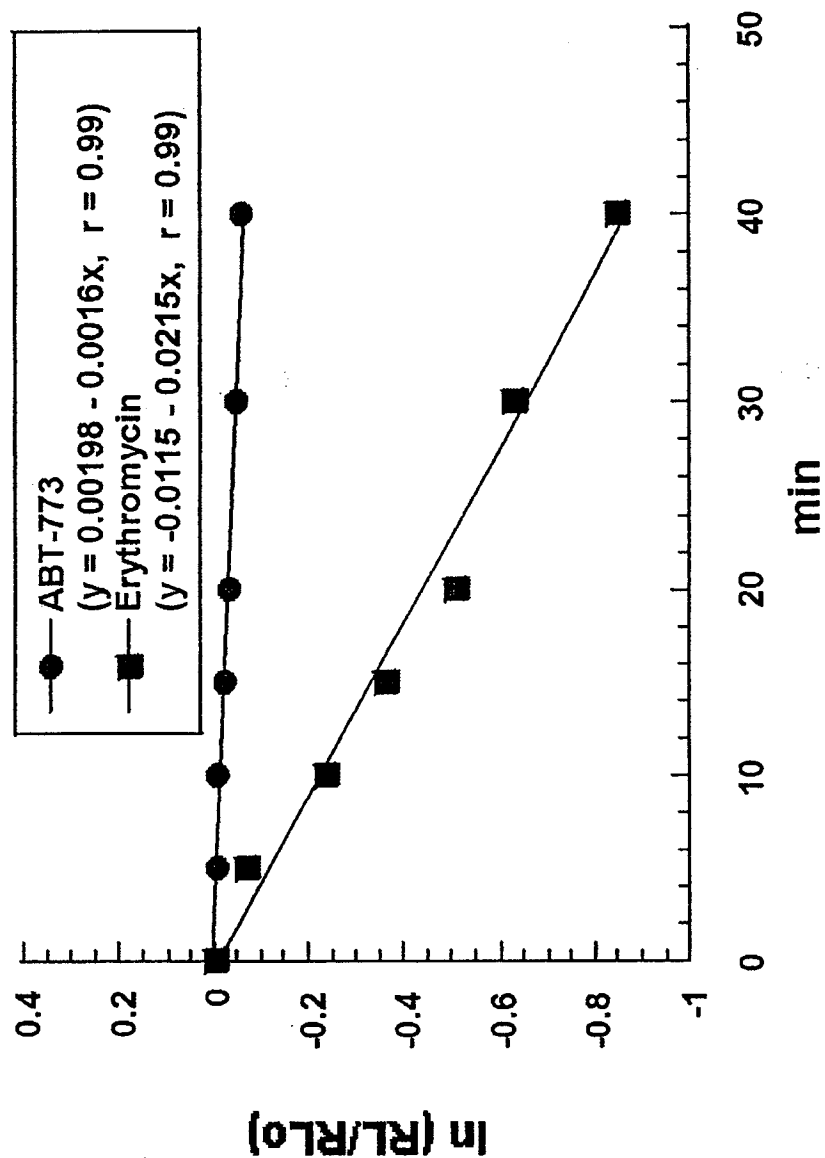


# Ribosome Binding, Susceptible *S. pneumoniae*

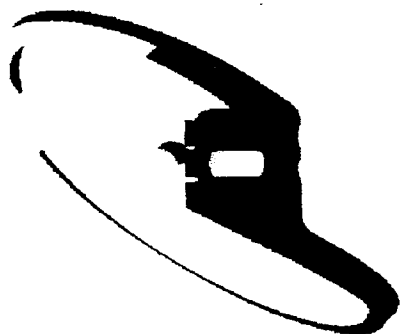




# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.



# QTc potential and Liver Toxicity Issues



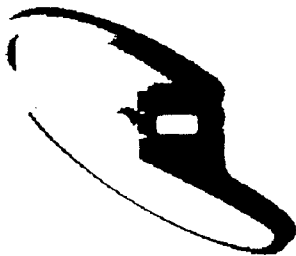
## QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
  - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
  - ICH guidelines require data from animal models and 200 patients
  - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
  - FDA has questioned whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QTc
  - Required to include ECG monitoring in pivotal Phase 3 studies
  - FDA may require a Phase I study in patients with underlying cardiac disease
  - Some antimicrobials now contain warnings for QT prolongation
  - Telithromycin (Ketek) data residing at FDA
    - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns



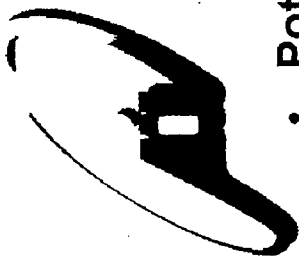
## QT<sub>c</sub> Prolongation Issues ABT-773

- Pre-clinical data positive for QT<sub>c</sub> dose response.
- A possible dose effect in Phase I at total daily dose  $\geq 800$  mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 C<sub>max</sub> 5X)
- No concentration response in Phase I studies ( $\leq 300$ mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)



## **QT<sub>c</sub> Prolongation Issues ABT-773 Plan**

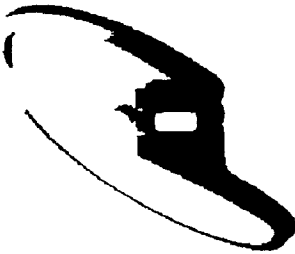
- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Planning FDA requested study of QTc in patients with pre-existing cardiac disease.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.



## Liver Toxicity Issues

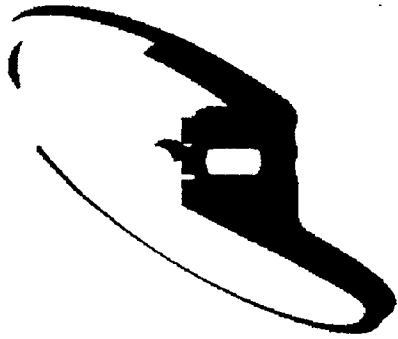
- Potential for liver toxicity is a concern for the FDA
  - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
  - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
  - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001





## **Liver Toxicity Issues for ABT-773**

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
  - Continue to monitor LFT in Phase III programs.
  - Jean Fox will attend FDA meeting.



# Phase III Program

# Phase III Program

## Proposed Indications and Treatment Duration

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to: <i>S. pyogenes</i> *	150 mg QD	5 d
Acute bacterial sinusitis due to: <i>H. influenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d
Acute bacterial exacerbation of chronic bronchitis due to: <i>H. influenzae</i> <i>H. parainfluenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i> **	150 mg 150 mg 150 mg 150 mg	5 d 5 d 5 d 5 d
Community-acquired pneumonia due to: <i>C. pneumoniae</i> <i>H. influenzae</i> <i>L. pneumophila</i> <i>M. pneumoniae</i> <i>S. pneumoniae</i> **	150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID 150 mg QD or BID	10 d 10 d 10 d 10 d 10 d

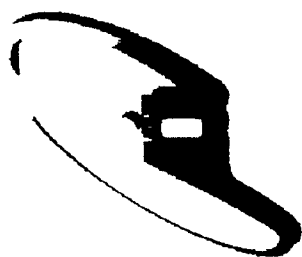
\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.



## Phase III Program Studies Started in Year 2000

Study	Indication	ABT-773 Regimen	Comparator	Number Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	185/520	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	0/520	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	131/600	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	0/500	EU (Non-IND)



## **Phase III Program Studies Started in Year 2000, Con't**

### **Dose Finding Studies for Sinusitis/CAP:**

<b>Study</b>	<b>Indication</b>	<b>ABT-773 Regimen</b>	<b>Comparator</b>	<b>Number Subjects</b>	<b>Location</b>
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	137/500	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	76/500	US, Canada, EU (IND)

# SDG Analysis of Ph. III CAP Development Options


CAP Development Strategy	Timeline Impact	Incremental Cost	Relative Regulatory Risk	Potential for 150 mg. QD in CAP
1. 150 mg QD only Ph. III (Begin now)	8/2002	0	High	Yes
2. Further Phase II 150x dose ranging, then Phase III	Parallel Phase II 150x dose ranging, then Phase III (8/2002)	\$5.4M	Low	Yes
3. Parallel Phase III program for 150 mg QD/150 mg BID	Parallel Phase III program for 150 mg QD/150 mg BID (8/2002)	\$5.4M	Low	Yes
4. 150 mg BID only Ph. III (Begin now)	8/2002	0	Mod	No
5. 300 mg QD only Ph. III (Begin now)	8/2002	0	Low	No
6. Phase III open-label dose ranging	8/2002	\$7.2M	Low	Yes

Selected Strategy

Positive Factor

Neutral Factor

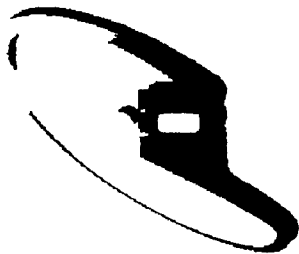
Negative Factor



## **Dosing Issue**

### **150 mg BID vs 150 mg QD: Background**

- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
  - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
  - few bacterial isolates, particularly with H. flu, in sinusitis
  - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, additional studies are ongoing to generate more data in these indications
  - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing

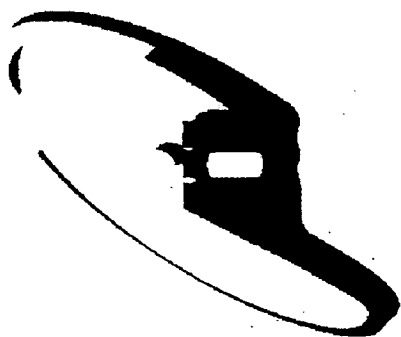


# Dosing Issue

## 150 mg BID vs 150 mg QD: Implications of Decision

- Regulatory and commercial environments differ dramatically between U.S. and ex-U.S.
  - For U.S., market:
    - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
    - Approval on indication-by-indication basis
    - Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis
  - For ex-U.S. market:
    - CAP data represents the “lynchpin” for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
    - Relatively minor commercial impact of BID dosing
    - Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis
- A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01
  - Data may not show a clear “winner” due to relatively low power of studies; may be a difficult decision
  - Due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision
- A plan to have divergent US/Ex-US clinical programs in CAP/sinusitis may be required to minimize regulatory / commercial risks
  - Cost / timeline implications





# ABT-773 IV Program

# Once-daily Zithromax® I.V. (azithromycin for injection)

The only I.V. advanced-generation  
macrolide for community-acquired  
pneumonia in adult hospitalized patients

Targeted coverage of the key pathogens of  
community-acquired pneumonia

Typical	Atypical
<i>Streptococcus pneumoniae</i>	<i>Legionella pneumophila</i>
<i>Haemophilus influenzae</i>	<i>Chlamydia pneumoniae</i>
<i>Staphylococcus aureus</i>	<i>Mycoplasma pneumoniae</i>
<i>Moraxella catarrhalis</i>	

Proven as effective as  
cefuroxime + erythromycin

Early step-down therapy to oral Zithromax

Very well tolerated

The most common side effects associated with treatment in adult patients who received I.V. Zithromax in studies of community-acquired pneumonia were diarrhea/constipation (4.3%), nausea (3.5%), abdominal pain (2.7%), and vomiting (1.1%). The most common side effects related to IV infusion included pain at the injection site (6.3%) and cold/flu-like symptoms (3.1%).

Zithromax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

Once-daily  
**Zithromax® I.V.**  
azithromycin for injection  
Pfizer Inc.  
The Power of Z in I.V.

The Power of  
**Z**  
in I.V.

\*Zithromax I.V. is indicated for community-acquired pneumonia due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Mycoplasma pneumoniae* in patients who require initial intravenous therapy.

In a controlled study of 201 hospitalized patients with community-acquired pneumonia, Zithromax (500 mg) as a single daily dose for the treatment course for 3 to 5 days followed by 500 mg/day for the oral treatment course for 7 to 10 days of therapy was compared with cefuroxime (750 mg) as a single daily dose for the treatment course for 3 to 5 days followed by 500 mg/day for the oral treatment course for 7 to 10 days of therapy. The results showed that patients treated with Zithromax I.V. had a significantly higher rate of clinical response to complete 7 to 10 days of therapy with or without erythromycin.

Please see brief summary of prescribing information on last page of this advertisement.



# ABT-773 IV Formulation Strategic, Commercial, and Technical Value

## • Strategic Value

- IV represents a channel not currently served by Anti-infective Franchise
- Leverages presence of Medical Center Reps and experience with ID community

## • Commercial Value

- IV availability figures favorably into decisions regarding formulary access to molecule
  - potential advantage over telithromycin, which will not have an IV
  - required to compete effectively with Zithromax, Tequin, Avelox which have IVs
- Positive impact on tablet formulation
  - estimated \$36MM incremental to peak tablet sales due to step-down therapy
  - Enhances overall “potency” image of brand

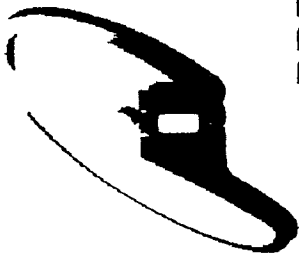
## • Technical Value

- Support for *S. pneumoniae* Resistance claim
  - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provides additional information on QT effects

IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value

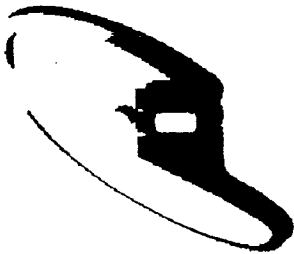
## **ABT-773 IV Program Formulation Objectives**

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.



## **ABT-773 IV Formulation PPD/HPD Funding Status**

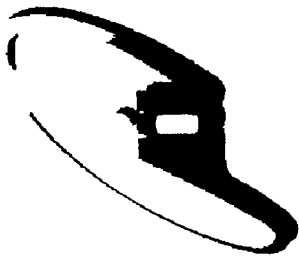
- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program
- 2001 funding
  - HPD first pass funding cut for 773 IV (\$7MM)
  - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)



## **ABT-773 IV Formulation**

### ***Animal Pain Study Results***

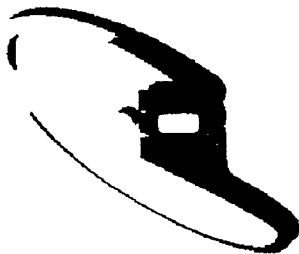
- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
  - Results not conclusive
  - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



## **ABT-773 IV Planned Clinical Program**

*With 2001 funding decision in Feb:*

- |  |         |
|--|---------|
| • Single Dose-rising Phase I study         | Apr/01  |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND                              | Oct/01  |
| • Initiate Phase III                       | Dec/01  |
| – 2 step-down CAP studies (US/Europe)      |         |
| – 2-3 days dosing                          |         |
| – Two seasons to complete                  |         |
| • Filing                                   | Aug/03  |

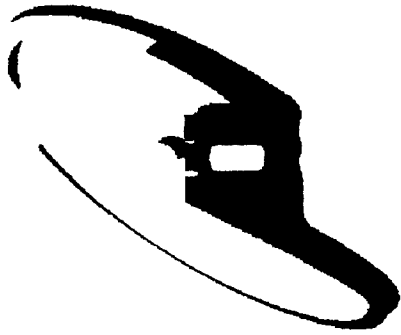


## ABT 773 IV Program Summary

- **Comments**

- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain, QT, GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant *S. pneumo* claim
- Total Program Cost 2000-2003 (\$22.5MM)





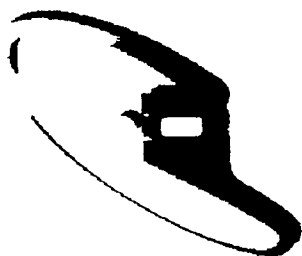
# Pediatric Program



## **ABT-773 Pediatric Formulation**

### **Importance to the 773 program**

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



## **ABT-773 Pediatric Program Formulation Objectives**

- Develop coated particle formulae for global use
  - coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.

# ABT 773 Pediatric Program

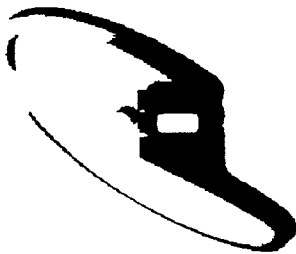
## Taste Assessment

### Sensory Analysis of Uncoated Drugs *Summary of Results*

The three drug substances can be ranked from most to least bitter as follows:

Drug Substance	Concentration (ppm) Which Exhibits an Initial Bitter Intensity $\leq 1$ (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

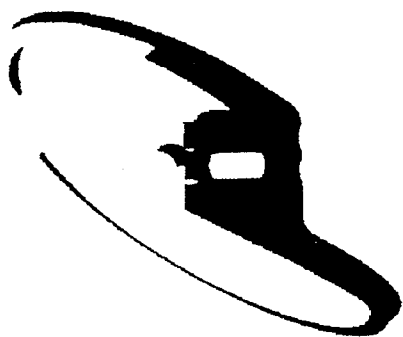
- ABT-773 is approximately five times more bitter than clarithromycin



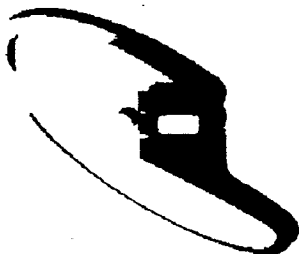
## **ABT 773 Pediatric Program**

### ***Taste Assessment***

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
  - Less bitter than Biaxin both initial and after taste
  - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the “concern” intensity level.

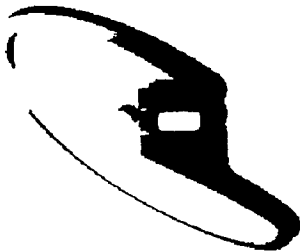


# Japan Program



## Japan Program Taisho

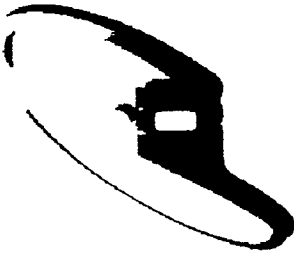
- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan



## Japan Program Clinical Plan

<ul style="list-style-type: none"><li>• Phase I in Japan<ul style="list-style-type: none"><li>– Food Effect Study</li><li>– Single and multiple dose study</li><li>– Review data (Abbott/Taisho)<ul style="list-style-type: none"><li>• PK data Japanese vs Caucasian</li><li>• Development program strategy</li></ul></li><li>– Present Kiko data and recommend development program May/01</li><li>– Start Tissue Conc. Study</li></ul></li></ul>	<u>Start</u> Completed  Completed  April/01    2Q/01
--	---





## **Japan Program Clinical Plan**

- PK similar in Japanese and Caucasians (12/02 filing)
  - Recommend to Kiko same dose in Japan as in ex-Japan
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
  - Phase II dose ranging study in CAP (Bridging study)
  - Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing





**Abbott Laboratories**

**Interoffice Correspondence**

From: Matt Russell  
PPD R&D Finance  
D-404, AP9 Ext. 5-3482  
Date: March 2, 2001

---

<b>TO:</b>	Bob Funck	D-404 AP9	Mike Higgins	D-404 AP9
	Tom Woidat	D-404 AP9	Mike Comilla	D-404 AP9
	Kirnes Holland	D-404 AP9	Paula Bourland	D-404 AP9
	Mischelle Vidakovic	D-404 AP9		

**Subject: 2001 PLAN FINAL Reference Package**

Attached you will find a copy of the 2001 PLAN FINAL Reference Package. This package has consolidated many of the key schedules we used in the PLAN. Hopefully, this will make referencing numbers from the PLAN easier for everyone. Please let me know if you have any questions.

**HIGHLY**

**CONFIDENTIAL  
ABBT 0037509**

# **2001 PLAN**

## ***FINAL Reference Package***

**Data as of February 16, 2001**

## 2001 PLAN Reference Package

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*Note: IDV's were issued in a separate package on 1/5/2001.*

# ***FINAL OpCost***

HIGHLY  
CONFIDENTIAL  
ARRT 0037512

2001 PLAN  
Pharmaceutical Products Research & Development  
Operating Cost Statement  
(\$000)

02/18/01  
08:37 AM

	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	01 PLAN VS 00 AGU
Pharmaceutical Discovery	134,725	134,688	145,324	---	(4,688)	(4,688)	140,636	(5,948)
-New Technology (accl # 742-505)	17,438	16,160	16,914	---	(4,468)	(4,468)	12,446	3,714
Total Pharmaceutical Discovery	152,163	150,848	162,238	---	(9,156)	(9,156)	153,082	(2,234)
Drug Safety Evaluation								
-Experimental Science	7,541	8,289	10,126	---	(1,507)	(1,507)	8,619	(330)
-Drug Safety Grants	---	970	1,640	---	(1,012)	(1,012)	628	342
-Clinical Drug Analysis	5,788	5,693	5,588	---	(459)	(459)	5,129	564
-Drug Safety Grants	---	671	385	---	(185)	(185)	200	471
-Toxicology	6,821	7,950	7,209	---	(740)	(740)	6,469	1,481
-Drug Safety Grants	---	3,511	2,188	---	(702)	(702)	1,486	2,025
-Pathology	3,617	3,901	3,597	---	127	127	3,724	177
-Drug Safety Grants	---	605	---	---	220	220	220	385
-Comparative Medicine	11,152	10,963	11,219	---	(197)	(197)	11,022	(59)
-Admin & Strategic	880	915	994	---	(87)	(87)	907	8
-Strategic & Exploratory Science	3,377	3,423	3,787	---	(345)	(345)	3,442	(19)
Total Drug Safety Evaluation	39,176	41,134	42,520	---	(3,208)	(3,208)	39,312	1,822
Medical Affairs								
- Genetics/Admin	4,161	4,619	5,645	---	(2,703)	(2,703)	2,942	1,677
- Medical Services	6,996	6,675	7,454	---	(56)	(56)	7,398	(723)
- Clinical Pharm	---	---	---	---	---	---	---	---
- Outcomes Res/Admin	1,430	1,358	1,542	---	201	201	1,743	(385)
- Phase IV	8,201	6,137	6,645	---	61	61	6,706	(569)
Total Medical Affairs	20,788	18,789	21,286	---	(2,497)	(2,497)	18,789	---
Information Mgmt & Technology								
- Resource Management	---	---	---	---	---	---	---	---
- Client Management	1,654	2,055	2,471	---	(7)	(7)	2,464	(409)
- Technology Management	44,502	44,763	48,529	---	(1,484)	(1,484)	47,045	(2,282)
- Emerging Tech Mgt	---	---	---	---	---	---	---	---
- I M & T Admin	715	558	840	---	---	---	840	(282)
Total Information Mgmt & Technology	46,871	47,376	51,840	---	(1,491)	(1,491)	50,349	(2,973)
Development Operations								
- Data Management	8,404	8,529	10,487	---	(3,368)	(3,368)	7,119	1,410
- Statistics	8,069	8,077	8,026	---	(1,590)	(1,590)	6,436	1,641
- Abbott Res & Lib Info Svcs-ARUS	3,093	3,243	3,807	---	(556)	(556)	3,251	(8)
Total Development Operations	19,566	19,849	22,320	---	(5,514)	(5,514)	16,806	3,043
Venture Management								
-Cardiovascular/Diabetes (CD)	55	172	122	---	(122)	(122)	---	172
-Anti - Infective	5,783	5,381	9,439	---	(707)	(707)	8,732	(3,351)
-Anti - Viral	13,597	9,491	10,203	---	262	262	10,465	(974)
-Analgesia/CCM	2,373	2,247	3,334	---	2,414	2,414	5,748	(3,301)
-Urology	2,629	2,660	3,750	---	(1,729)	(1,729)	2,021	638
-Molecular Therapeutics	2,839	3,102	---	---	---	---	---	3,102
-Neuroscience/Quinolones	---	---	---	---	---	---	---	---
-Oncology & Transplant (Cancer Mgmt)	6,450	6,655	6,574	---	810	810	7,384	(729)
Total Venture	33,726	29,708	33,422	---	928	928	34,350	(4,842)
Administration	16,853	18,312	20,312	---	(660)	(660)	19,652	(1,340)
Pharm Analytical R&D	62,454	63,142	62,721	---	(3,868)	(3,868)	58,853	4,289
Regulatory Affairs	9,119	9,008	10,070	---	(648)	(648)	9,422	(414)
Phase-1 Center	8,990	8,585	14,068	---	(4,398)	(4,398)	9,670	(1,085)
Total Functional	409,706	406,751	440,797	---	(30,512)	(30,512)	410,285	(3,234)
Inf1 - Manpower	3,560	3,988	6,567	(2,462)	---	(2,462)	4,105	(117)
Clinical Grants								
-Domestic	103,780	109,231	139,785	(26,467)	4,710	(21,757)	118,028	(8,797)
-Adjustment	---	(846)	---	---	---	---	---	(846)
Total Clinical Grants	103,780	108,385	139,785	(26,467)	4,710	(21,757)	118,028	(9,643)
Services Purchased	52,599	57,834	63,226	(6,127)	(9,627)	(15,954)	47,272	10,562
SPD Purchases	54,991	63,921	63,467	(5,110)	(4,522)	(10,032)	53,435	10,486
Corporate Task	---	---	8,100	---	(8,100)	(8,100)	---	---
Judgment - Internal	---	(10,930)	(27,894)	20,977	12,977	33,954	6,060	(16,990)
Judgment - Published	---	(3,642)	(30,100)	5,000	15,300	20,300	(9,800)	6,158
Gabitril reimbursement from Commercial	---	---	---	---	---	---	---	---
Hand Pos/Flash to Actual Adjustment	---	---	---	---	---	---	---	---
Other Project Changes:	---	---	---	---	---	---	---	---
Total Project Changes (For Exp Cat)	---	---	---	---	---	---	---	---
Total Gross Expense	624,636	626,307	663,948	(14,189)	(20,374)	(34,563)	629,385	(19,722)
Services Sold	(249,043)	(251,577)	(253,911)	(2,411)	12,304	9,893	(244,018)	(7,559)
Net Total	375,593	374,730	410,037	(16,600)	(8,070)	(24,670)	385,367	(10,637)
Target	375,593	374,730	410,037	(16,600)	(8,070)	(24,670)	385,367	(10,637)

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2001 PLAN  
Pharmaceutical Products Research & Development  
Services Purchased  
(\$000)

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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	2001 PLAN	01 PLAN VS 00 AGU
Patents & Trademark	5,564	5,565	5,976	74		74	6,050	(485)
Satellite Copy Charges	556	555	549	(10)		(10)	539	16
Corp Admin Fixed	4,880	4,995	5,126	102	217	319	5,445	(450)
Corp Cost Pools	5,031	5,175	5,231	(102)	(59)	(161)	5,070	105
CHMD Services Purchased Fixed (AHD)	193	197	197	(1)		(1)	196	1
PPD Ops Fixed Allocations	2,607	2,522	3,232				3,232	(710)
CENG - Fixed Maintenance from PPD Op	948	947	899				899	48
CHEN Variable (EWRS)	323	141	147				147	(8)
CMIS - Purchasing	697	697	733	14		14	747	(50)
CHMS Telecommunications	116	116	116	2	12	14	130	(14)
Fixed L C Exp - Admin Services	415	410	427	(1)	(5)	(6)	421	(11)
Corp Eng EHS Fixed Allocation	559	558	597				597	(39)
<b>TOTAL CORPORATE ALLOCATION</b>	<b>21,869</b>	<b>21,878</b>	<b>23,230</b>	<b>78</b>	<b>165</b>	<b>243</b>	<b>23,473</b>	<b>(1,595)</b>
CMIS - Unit of Activity, Fixed - Other	3,012	2,263	3,861	(747)	(447)	(1,194)	2,667	(404)
CMIS - Unit of Activity, Fixed - Aegis	2,062	2,890	2,100				2,100	790
PPD Personnel D0A47	2,512	2,456	2,600		1	1	2,601	(145)
PPD Mfg Ops - Allocation	60	60	60	3		3	63	(3)
PPD Ops QA Int Svcs/Reg Affairs	1,438	1,438	1,942				1,942	(504)
PPD Ops Returned Goods	130	131	136				136	(5)
Project Expense (\$1MM)	10,815	11,208	11,208	(614)	(3,495)	(4,109)	7,099	4,109
<b>TOTAL BURDEN FILE</b>	<b>41,898</b>	<b>42,324</b>	<b>45,137</b>	<b>(1,280)</b>	<b>(3,776)</b>	<b>(5,056)</b>	<b>40,081</b>	<b>2,243</b>
SPD Pilot Plant Stack Card	20,926	20,960	21,195	4,632	(1,330)	3,302	24,497	(3,537)
SPD Bulk Direct	24,905	33,681	32,992	(12,674)	(2,990)	(15,664)	17,328	16,353
Excess Capacity Stack Card	9,160	9,280	9,280	2,932	(602)	2,330	11,610	(2,330)
<b>Subtotal SPD (Other than TAP)</b>	<b>54,991</b>	<b>63,921</b>	<b>63,467</b>	<b>(5,110)</b>	<b>(4,922)</b>	<b>(10,032)</b>	<b>53,435</b>	<b>10,486</b>
Grant/Out of Pocket Purchases:								
TAP Bulk Drug (D-TAP)	17	125	125	(41)		(41)	84	41
TAP - SPD Manpower & Bulk (D-453)	211	450	450	(205)		(205)	245	205
Pharmacogenetics - ADD Allocation								
Misc Expense								
<b>Subtotal (For Exp Cat)</b>	<b>228</b>	<b>575</b>	<b>575</b>	<b>(246)</b>		<b>(246)</b>	<b>329</b>	<b>246</b>
Other Purchases:								
Clari Once-A-Day (Global AI Manpower)	10,189	11,393	11,677	2	(3,916)	(3,914)	7,763	3,630
Corp Drug User Fees	1,918	1,951	1,838	(631)		(631)	1,207	744
Patent to Operations (search services)	200	200						200
D-A54 Floor Space (not in functionals)	377	405			182	182	182	223
D-A54 Deprec (not in functionals)	(501)	1,864	3,033		(49)	(49)	2,984	(1,120)
Molecular Probes	(6)	7	7				7	
Inventory transfer for Protease 2nd Gen		(5,726)						(5,726)
SDG/Other	877	8,287	5,000	(5,000)		(5,000)		8,287
Clinical Supplies (Tricia Geran -PPD Ops)	5	200	200				200	
Aegis Charges	226							
Library (D441) to CHMS								
QA (D44N) to Operations	1,367	1,446	1,500				1,500	(54)
Sangstat (Cyclosporine)		(2,400)	(360)		360	360		(2,400)
Sangstat (Sangcya)		967						967
Gabitril Royalty								
Ritonavir/LaRoche Combo								
NOVO Settlement	(1,500)	(1,500)						(1,500)
Metabolex	(888)	(888)						(888)
FLAP/Vanguard	(818)	(818)						(818)
Sanofi Cost Sharing w/Gabitril		(150)						(150)
CI charge from OPS (Cin Val Mgr) + \$49		171						171
Contract Management System	47							
HPD R&D Purchased	411							
Yale Univ. - Survivan Patent	2							
Staples Rebates	(66)							
Triangle receipt \$2,935 +\$325 for1999	(3,462)	(2,914)	(5,381)				(5,381)	2,467
Sertindole License								
Comdisco	2,440	2,440						2,440
Hydrocodone (IDV-in from HPD)				4,028	(4,028)			
CRO Rebates	(381)			(3,000)		(3,000)	(3,000)	3,000
Gabitril Reimbursement from Commercial					1,400	1,400	1,400	(1,400)
Other	36							
<b>Subtotal (For Exp Cat)</b>	<b>10,473</b>	<b>14,935</b>	<b>17,514</b>	<b>(4,601)</b>	<b>(6,051)</b>	<b>(10,652)</b>	<b>6,862</b>	<b>8,073</b>
<b>Grand Total</b>	<b>107,590</b>	<b>121,755</b>	<b>126,693</b>	<b>(11,237)</b>	<b>(14,749)</b>	<b>(25,986)</b>	<b>100,707</b>	<b>21,048</b>

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2001 PLAN  
Pharmaceutical Products Research & Development  
Services Sold  
(\$000)

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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	2001 PLAN	01 PLAN VS 00 AGU
General Benefit								
-Global Pharmaceutical	183,768	183,768	193,857	4,813	(12,000)	(7,187)	186,670	(2,902)
Direct Sister Benefit								
-R&D Sci Serv.	3,619	4,478	2,571	55	(242)	(187)	2,384	2,094
-Direct Service	4,125	3,794	3,975	(175)	...	(175)	3,800	(6)
Total Direct Support	7,744	8,272	6,546	(120)	(242)	(362)	6,184	2,088
Total Int'l Sister Div.	191,512	192,040	200,403	4,693	(12,242)	(7,549)	192,854	(814)
TAP Judgment (Positive Controls)								
TAP Bulk Drug (D-TAP)	17	125	125	(41)	...	(41)	84	41
TAP - SPD Manpower & Bulk	211	450	450	(205)	...	(205)	245	205
TAP - All Other	20,715	23,359	20,170	(575)	261	(314)	19,856	3,503
Total TAP (Incl. Judgment)	20,943	23,934	20,745	(821)	261	(560)	20,185	3,749
Domestic Sister Divisions:								
HPD	9,442	10,575	9,689	(950)	95	(855)	8,834	1,741
ADD	2,268	1,896	2,340	43	...	43	2,383	(487)
SPD	4,312	4,684	4,810	(719)	818	99	4,909	(225)
ROSS	186	663	1,851	40	64	104	1,955	(1,292)
CPD	3	39	42	...	...	...	42	(3)
MIS	69	71	69	5	...	5	74	(3)
AHD	...	...	...	...	...	...	...	...
CHMS Library Services	...	...	...	...	...	...	...	...
Corp. Eng.	20	2	...	...	...	...	...	2
Subtotal	16,300	17,930	18,801	(1,581)	977	(604)	18,197	(287)
Other Sister Divisions:								
Corp. Admin.								
-Corp. Admin.	71	42	23	1	...	1	24	18
-Tap Rate Diff	461	461	485	...	...	...	485	(24)
-Symposium Expense	155	155	165	...	...	...	165	(10)
Subtotal CHAD	687	658	673	1	...	1	674	(16)
PPD Product R&D:								
Mfg Support (MC,PM)	14,283	10,780	12,096	119	...	119	12,215	(1,435)
Mfg Support (PV)	124	285	263	...	...	...	263	22
PPD Marketing (P5,P6)	4,658	5,414	4,920	...	(1,300)	(1,300)	3,620	1,794
Subtotal Other	19,065	16,479	17,279	119	(1,300)	(1,181)	16,098	381
VAT Refund	537	537	...	...	...	...	...	537
PARD Services Sold Impact (Judgement)	...	...	(3,990)	...	...	...	(3,990)	3,990
Rounding	(1)	(1)	...	...	...	...	...	(1)
Grand Total	249,043	251,577	253,911	2,411	(12,304)	(9,893)	244,018	7,559

## Memo:

INPUT Global AI from DetRoll file	N/A	183,768	193,857	N/A	N/A	N/A	186,670
Calculated above	N/A	183,768	193,857	N/A	N/A	N/A	186,670
Key Check (s/b 0)	N/A	...	...	N/A	N/A	N/A	...
INPUT From J:\Drive File	N/A	210,626	219,877	N/A	N/A	N/A	211,725
Calculated above	N/A	210,628	219,877	N/A	N/A	N/A	211,725
Key Check (s/b 0)	N/A	(2)	...	N/A	N/A	N/A	...
Sister Division Amount							
INPUT From DetRoll file	N/A	67,809	64,044	N/A	N/A	N/A	61,338
Calculated above	N/A	67,809	60,054	N/A	N/A	N/A	57,348
Key Check (s/b 0)	N/A	...	3,990	N/A	N/A	N/A	3,990
Sister Division Reconciliation							
Sister Division Memos -Oracle	N/A	67,809	60,054	N/A	N/A	N/A	57,348
BP - Blue Plans	N/A	49,144	57,354	N/A	N/A	N/A	104,224
DC - Div Computing/Systems	N/A	13,730	13,850	N/A	N/A	N/A	20,079
DO - Department Overhead	N/A	50	50	N/A	N/A	N/A	50
GO - Global Delivery	N/A	328,237	345,312	N/A	N/A	N/A	299,564
GD - Global Discovery	N/A	96,719	90,107	N/A	N/A	N/A	94,827
P1 - Pharmaceutical Products	N/A	44,693	59,654	N/A	N/A	N/A	38,962
TG - Triangle	N/A	3,011	5,461	N/A	N/A	N/A	5,461
TAP Pass Thru & Bulk Drug not in Orac	N/A	...	...	N/A	N/A	N/A	...
Other Judgement	N/A	...	...	N/A	N/A	N/A	3,990
Total	N/A	603,393	631,842	N/A	N/A	N/A	624,505
INPUT Total Per Oracle	N/A	600,093	631,253	N/A	N/A	N/A	624,471
Variance	N/A	3,300	589	N/A	N/A	N/A	34

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2001 PLAN  
Pharmaceutical Products Research & Development  
Clinical Grants  
(\$000's)

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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	01 PLAN VS 00 AGU
<b>PPD SERVICE:</b>								
Tiagabine/Gabitril	(80)	2,600	1,900	...	(1,900)	(1,900)	...	2,600
Omnicef	...	...	4,800	(2,000)	200	(1,800)	3,000	(3,000)
Depakote/Depakene	15,319	14,589	11,174	...	(1,733)	(1,733)	9,441	5,148
r-Pro-UK	(45)	(45)	...	...	...	...	...	(45)
Fenofibrate (Foumier)	799	(160)	2,250	...	(2,211)	(2,211)	39	(199)
Hematin	407	...	...	...	600	600	600	(600)
PharmacoGenetics (Genset)	...	200	200	...	...	...	200	...
<b>TOTAL PPD SERVICE</b>	<b>16,400</b>	<b>17,184</b>	<b>20,324</b>	<b>(2,000)</b>	<b>(5,044)</b>	<b>(7,044)</b>	<b>13,280</b>	<b>3,904</b>
<b>GLOBAL SERVICE:</b>								
Ritonavir ABT-538	2,715	4,382	1,752	...	(508)	(508)	1,244	3,138
Protease 2nd Gen ABT-378	30,884	30,362	13,379	...	9,196	9,196	22,575	7,787
Dopamine	...	...	...	...	...	...	...	...
KCO ABT-598	...	...	...	...	380	380	380	(380)
ABT-594 (formerly CCM)	2,106	2,800	13,760	(13,051)	356	(12,695)	1,065	1,735
ABT-089 (formerly ChCM)	...	...	1,628	...	(1,628)	(1,628)	...	...
Clarithromycin	2,314	4,448	4,210	...	(1,270)	(1,270)	2,940	1,508
Ketolide ABT-773	23,093	23,137	46,382	...	1,023	1,023	47,405	(24,268)
Prokinetic Macrolide - Dom	...	...	...	...	...	...	...	...
Zileuton & 2nd Generation	...	...	...	...	...	...	...	...
BPH ABT-980	13,855	14,058	16,678	(11,416)	(5,262)	(16,678)	...	14,058
Cyclosporine	7,831	7,560	1,300	...	(307)	(307)	993	6,567
H2G (Medivir)	63	...	...	...	...	...	...	...
Endothelin	2,066	2,440	8,794	...	10,457	10,457	19,251	(16,811)
NS 49 Nippon Shinyakkyu ABT-23	357	633	...	...	...	...	...	633
Bimocromol (Biorex)	...	...	...	...	...	...	...	...
Anti-Mitotic ABT-751	...	...	2,091	...	(1,066)	(1,066)	1,025	(1,025)
Hytrin	...	...	...	...	...	...	...	...
FTI (Farnesyltransferase)	...	...	...	...	...	...	...	...
MMPI (Metalloprotease)	116	231	1,346	...	(228)	(228)	1,118	(887)
Taxane	...	...	...	...	...	...	...	...
TSP Peptide	843	968	1,710	...	(89)	(89)	1,621	(653)
Quinolone	680	638	5,000	...	...	...	5,000	(4,362)
Cox II	157	131	784	...	(653)	(653)	131	...
Neuraminidase	123	...	...	...	...	...	...	...
Adjustment (EVR)	...	(846)	...	...	...	...	...	(846)
<b>TOTAL GLOBAL SERVICE</b>	<b>87,203</b>	<b>90,942</b>	<b>118,814</b>	<b>(24,467)</b>	<b>10,401</b>	<b>(14,066)</b>	<b>104,748</b>	<b>(13,806)</b>
<b>MISC:</b>								
Vitamin D Analog/Iron Dextran	...	76	...	...	...	...	...	76
Isotretinoin/Norvir Investigation	...	...	...	...	...	...	...	...
Adjustments	...	...	...	...	...	...	...	...
Dexmedetomidine/Zemplar (HPD)	177	183	647	...	(647)	(647)	...	183
Tranxene Reformulation	...	...	...	...	...	...	...	...
Biaxin Reformulation	...	...	...	...	...	...	...	...
	177	259	647	...	(647)	(647)	...	259
<b>GRAND TOTAL GRANTS</b>	<b>103,780</b>	<b>108,385</b>	<b>139,785</b>	<b>(26,467)</b>	<b>4,710</b>	<b>(21,757)</b>	<b>118,028</b>	<b>(9,643)</b>

**2001 PLAN**  
**Pharmaceutical Products Research & Development**  
**Operating Cost Statement**  
**(\$000)**

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	2000 ACTUALS	09/25/00 FINAL 00 AGU	Book I ORACLE 2001 PLAN	10/24/2000 PRIOR ADJS	12/01/00-1/30/00 CURRENT ADJS	TOTAL ADJS	FINAL 2001 PLAN	01 PLAN VS 00 AGU
SDG/Other	877	1,500	3,000	(3,000)		(3,000)	...	1,500
HIV/Knoll/QD/Other	...	1,000	...			...	...	1,000
Aegis Insurance	...	952	...			...	...	952
Genset #1	...	500	...			...	...	500
IT Productivity Projects	...	...	2,000	(2,000)		(2,000)	...	...
Neurosearch FTE \$2530, depr \$20	...	...	...			...	...	...
Coactinon	...	...	...			...	...	...
SPD IDV Liponavir	...	607	...			...	...	607
Triangle R&D	...	...	...			...	...	...
Data Management Absorbition	...	1,078	...			...	...	1,078
Other New Products	...	2,650	...			...	...	2,650
Quinolone In License Payment	...	...	...			...	...	...
Division Task	...	...	...	...		...	...	...
HPD R&D Purchased	...	...	...			...	...	...
<b>Total SDG/Other</b>	<b>877</b>	<b>8,287</b>	<b>5,000</b>	<b>(5,000)</b>	<b>...</b>	<b>(5,000)</b>	<b>...</b>	<b>8,287</b>

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PPRD FUNCTIONAL EXPENSE  
RECONCILIATIONS MONTH - \$  
2001 PLAN02/18/01  
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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Discovery Deals * (742-505)	12,448	...	625	2,015	250	625	2,015	250	625	2,015	250	625	3,151	12,448
All Other Discovery *	140,638	11,461	11,481	11,507	11,527	11,575	11,614	11,614	11,962	12,018	12,036	12,056	11,785	140,636
Subtotal Pharmaceutical Discovery	153,082	11,461	12,106	13,522	11,777	12,200	13,629	11,864	12,587	14,033	12,286	12,681	14,936	153,082
<b>DRUG SAFETY</b>														
Experimental Science	8,619	689	697	714	715	716	732	733	734	721	722	723	723	8,619
Drug Safety Grants (742-200)	628	52	52	52	52	52	52	52	52	53	53	53	53	628
Clinical Drug Analysis	5,129	423	423	424	425	425	431	432	432	428	428	429	429	5,129
Drug Safety Grants	200	17	17	17	17	17	17	17	17	16	16	16	16	200
Toxicology	6,469	524	525	537	537	538	544	545	546	542	543	544	544	6,469
Drug Safety Grants	1,486	124	124	124	124	124	124	124	124	124	124	124	122	1,486
Pathology	3,724	299	300	307	307	308	319	320	320	310	311	311	312	3,724
Drug Safety Grants	220	18	18	18	18	18	18	18	18	19	19	19	19	220
Comparative Medicine	11,022	916	916	917	917	918	918	919	919	920	920	921	921	11,022
Admin & Strategic	907	75	75	75	75	75	75	76	76	76	76	76	77	907
Strategic & Exploratory Science	3,442	284	284	285	285	285	290	290	291	287	287	288	286	3,442
Subtotal Drug Safety	39,312	3,210	3,220	3,259	3,261	3,265	3,309	3,315	3,318	3,284	3,287	3,292	3,292	39,312
<b>MEDICAL AFFAIRS</b>														
Administration (Clin Res - CNS)	2,942	226	227	227	247	248	255	255	256	250	250	251	250	2,942
Medical Services	7,398	596	601	612	614	617	618	620	621	623	624	625	627	7,398
Outcomes Research	1,743	124	124	138	139	139	153	153	154	154	154	155	158	1,743
Phase IV	6,708	497	526	546	556	557	567	573	575	576	577	578	578	6,708
Subtotal Medical Affairs	18,789	1,443	1,478	1,523	1,558	1,581	1,593	1,801	1,806	1,803	1,805	1,809	1,811	18,789
<b>Information Mgmt &amp; Technology</b>														
Resource Management	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Client Management	2,484	203	204	204	205	205	205	206	207	207	207	208	203	2,484
Technology Management	47,045	3,576	3,321	3,472	3,351	3,518	3,433	3,784	3,673	3,642	4,554	4,492	8,229	47,045
I M & T Admin	840	69	69	69	70	70	70	70	70	70	71	71	71	840
Subtotal Information Mgmt & Tech	50,349	3,848	3,594	3,745	3,628	3,793	3,708	4,060	3,950	3,919	4,832	4,771	6,503	50,349
<b>Development Operations</b>														
Data Management	7,119	588	589	590	591	592	593	594	595	596	597	597	597	7,119
Statistics	6,436	525	526	527	528	530	539	541	542	543	544	545	548	6,436
Abbott Res & Lib Info Svcs-ARLIS	3,251	266	266	266	248	249	256	256	256	257	257	248	426	3,251
Subtotal Development Operations	16,806	1,379	1,381	1,383	1,367	1,371	1,388	1,391	1,393	1,396	1,398	1,390	1,569	16,806
<b>VENTURE MANAGEMENT</b>														
Cardiovascular/Diabetes (CD)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Anti-Infective	8,732	453	467	468	479	480	481	482	3,482	484	485	486	485	8,732
Anti-Viral	10,485	867	868	869	870	871	872	873	873	874	875	876	877	10,485
Analgesia/CCM	5,748	494	499	499	499	500	501	501	450	451	451	451	452	5,748
Urology	2,021	167	167	167	168	168	168	169	169	169	170	170	170	2,021
Molecular Therapeutics	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Neuroscience	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Oncology	7,384	577	578	579	594	617	652	628	629	631	632	632	635	7,384
Subtotal Venture	34,350	2,558	2,579	2,582	2,610	2,636	2,674	2,653	5,603	2,609	2,612	2,615	2,619	34,350
Administration	19,652	1,626	1,629	1,631	1,633	1,635	1,637	1,639	1,641	1,643	1,645	1,647	1,646	19,652
PARD	58,853	4,890	4,881	4,967	4,939	4,971	5,045	4,991	5,042	4,992	5,059	5,045	4,031	58,853
Regulatory Affairs	9,422	673	699	766	786	798	800	811	812	814	815	817	831	9,422
Phase-1 Center	9,670	764	772	777	812	813	815	816	817	819	820	821	824	9,670
<b>TOTAL FUNCTIONAL</b>	410,285	31,852	32,339	34,155	32,367	33,043	34,598	33,141	36,769	35,112	34,359	34,688	37,862	410,285
International Manpower	4,105	287	369	205	287	369	248	452	452	452	431	411	144	4,105
Clinical Grants	118,028	8,273	8,232	10,105	10,456	10,626	11,508	9,804	10,811	10,016	6,787	10,766	10,646	118,028
QA54 Services Purchased	100,707	9,075	9,075	8,268	8,742	8,252	6,907	8,252	8,252	8,113	8,717	8,717	8,337	100,707
Corporate Task	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Judgment - Internal	6,060	5,668	2,909	1,944	1,289	2,290	4,725	(1,565)	(3,054)	(2,135)	599	(1,383)	(5,227)	6,060
Judgment - Published	(9,800)	(817)	(817)	(817)	(817)	(817)	(817)	(817)	(817)	(816)	(816)	(816)	(816)	(9,800)
Gabitril reimbursement from Comm	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Hand Post/Flash to Actual Adjustment	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Other Project Changes:	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Gross PPD R&amp;D Expense</b>	629,385	54,338	52,107	53,860	52,324	53,763	57,165	49,267	52,413	50,742	50,077	52,383	50,946	629,385
QA55 Services Sold	(244,018)	(21,165)	(20,215)	(20,854)	(20,326)	(20,715)	(21,963)	(19,061)	(20,005)	(19,703)	(19,579)	(20,455)	(19,977)	(244,018)
<b>Net PPD R&amp;D Expense</b>	385,367	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Memo: Quarterly Net Expense	...	...	98,071	...	...	...	100,248	...	...	93,653	...	93,395	24,244	...
This line is input judgment plugs to this #.	385,367	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
		8.61%	8.28%	8.56%	8.30%	8.58%	9.13%	7.84%	8.41%	8.05%	7.91%	8.29%	8.04%	385,367
<b>2000 Final AGU</b>	32,133	30,404	35,911	33,138	32,058	45,704	28,013	27,124	29,769	26,703	27,355	26,418	374,730	...
<b>2000 Actuals</b>	32,133	30,404	35,911	33,138	32,058	45,704	28,013	27,124	29,388	27,095	27,115	27,512	375,593	...
<b>1999 Actuals (Adjusted for Thermbolytics)</b>	21,427	23,693	25,358	24,205	25,870	24,286	25,642	24,019	23,961	28,343	27,940	40,699	315,443	...
<b>1998 Actuals</b>	21,582	23,967	27,222	25,213	23,774	25,666	24,495	23,269	26,430	33,783	24,554	42,270	322,225	...

\* Do not report these lines for actuals; report only Total Pharmaceutical Discovery line. Detail is shown here for planning purposes only.

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PPRD FUNCTIONAL EXPENSE  
RECONCILIATIONS YTD - \$  
2001 PLAN

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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Discovery Deals * (742-505)	12,446	...	625	2,840	2,890	3,515	5,530	5,780	6,405	8,420	8,670	9,295	12,446
All Other Discovery *	140,636	11,461	22,942	34,449	45,976	57,551	69,165	80,779	92,741	104,759	116,795	128,851	140,636
Subtotal Pharmaceutical Discovery	153,082	11,461	23,567	37,089	48,866	61,066	74,695	86,559	99,146	113,179	125,465	138,146	153,082
<b>DRUG SAFETY</b>													
Experimental Science	8,619	689	1,386	2,100	2,815	3,531	4,263	4,996	5,730	6,451	7,173	7,896	8,619
Clinical Drug Analysis	5,129	423	846	1,270	1,695	2,120	2,551	2,983	3,415	3,843	4,271	4,700	5,129
Toxicology	6,469	524	1,049	1,586	2,123	2,661	3,205	3,750	4,296	4,838	5,381	5,925	6,469
Pathology	3,724	299	599	906	1,213	1,521	1,840	2,160	2,480	2,790	3,101	3,412	3,724
Comparative Medicine	11,022	916	1,832	2,749	3,666	4,584	5,502	6,421	7,340	8,260	9,180	10,101	11,022
Admin & Strategic	907	75	150	225	300	375	450	528	602	678	754	830	907
Strategic & Exploratory Science	3,442	284	568	853	1,138	1,423	1,713	2,003	2,294	2,581	2,868	3,156	3,442
Subtotal Drug Safety	39,312	3,210	6,430	9,889	12,950	16,215	19,524	22,839	26,157	29,441	32,728	36,020	39,312
<b>MEDICAL AFFAIRS</b>													
Administration (Clin Res - CNS)	2,942	226	453	680	927	1,175	1,430	1,685	1,941	2,191	2,441	2,692	2,942
Medical Services	7,398	596	1,197	1,809	2,423	3,040	3,658	4,278	4,899	5,522	6,146	6,771	7,398
Outcomes Research	1,743	124	248	386	525	664	817	970	1,124	1,278	1,432	1,587	1,743
Phase IV	6,706	497	1,023	1,509	2,125	2,682	3,249	3,822	4,397	4,973	5,550	6,128	6,706
Subtotal Medical Affairs	18,789	1,443	2,921	4,444	6,000	7,561	9,154	10,755	12,361	13,964	15,569	17,178	18,789
<b>Information Mgmt &amp; Technology</b>													
Resource Management	...	...	...	...	...	...	...	...	...	...	...	...	...
Client Management	2,464	203	407	611	816	1,021	1,226	1,432	1,639	1,846	2,053	2,261	2,464
Technology Management	47,045	3,578	6,897	10,389	13,720	17,238	20,671	24,455	28,128	31,770	36,324	40,818	47,045
IM & T Admin	840	69	138	207	277	347	417	487	557	627	698	769	840
Subtotal Information Mgmt & Tech	50,349	3,848	7,442	11,187	14,813	18,606	22,314	26,374	30,324	34,243	39,075	43,846	50,349
<b>Development Operations</b>													
Data Management	7,119	588	1,177	1,767	2,358	2,950	3,543	4,137	4,732	5,328	5,925	6,522	7,119
Statistics	6,436	525	1,051	1,578	2,106	2,636	3,175	3,716	4,258	4,801	5,345	5,890	6,436
Abbott Res & Lib Info Svcs-ARLIS	3,251	266	532	798	1,046	1,295	1,551	1,807	2,063	2,320	2,577	2,825	3,251
Subtotal Development Operations	16,806	1,379	2,760	4,143	5,510	6,881	8,269	9,660	11,053	12,449	13,847	15,237	16,806
<b>VENTURE MANAGEMENT</b>													
Cardiovascular/Diabetes (CD)	...	...	...	...	...	...	...	...	...	...	...	...	...
Anti-Infective	8,732	453	920	1,388	1,867	2,347	2,828	3,310	3,792	4,276	4,761	5,247	5,732
Anti-Viral	10,465	867	1,735	2,604	3,474	4,345	5,217	6,090	6,963	7,837	8,712	9,588	10,465
Analgesia/CCM	5,748	494	993	1,492	1,991	2,491	2,992	3,493	3,994	4,495	4,996	5,497	5,998
Urology	2,021	167	334	501	669	837	1,005	1,174	1,343	1,512	1,681	1,851	2,021
Molecular Therapeutics	...	...	...	...	...	...	...	...	...	...	...	...	...
Neuroscience	...	...	...	...	...	...	...	...	...	...	...	...	...
Oncology	7,384	577	1,155	1,734	2,328	2,945	3,597	4,225	4,854	5,485	6,117	6,749	7,384
Subtotal Venture	34,350	2,558	5,137	7,719	10,329	12,965	15,639	18,292	20,955	23,608	26,261	28,914	31,567
Administration	19,652	1,626	3,255	4,886	6,519	8,154	9,791	11,430	13,071	14,714	16,359	18,006	19,652
PARD	58,853	4,890	9,771	14,738	19,677	24,648	29,693	34,684	39,726	44,718	49,777	54,822	58,853
Regulatory Affairs	9,422	673	1,372	2,138	2,924	3,722	4,522	5,333	6,145	6,959	7,774	8,591	9,422
Phase-1 Center	9,670	764	1,536	2,313	3,125	3,938	4,753	5,569	6,386	7,205	8,025	8,846	9,670
<b>TOTAL FUNCTIONAL</b>	<b>410,285</b>	<b>31,852</b>	<b>64,191</b>	<b>98,346</b>	<b>130,713</b>	<b>163,756</b>	<b>198,354</b>	<b>231,495</b>	<b>268,264</b>	<b>303,376</b>	<b>337,735</b>	<b>372,423</b>	<b>410,285</b>
Memo: % of Total Func, excl. Disc Deals		8.0%	16.0%	24.1%	32.1%	40.3%	48.5%	56.7%	65.8%	74.1%	82.7%	91.3%	100.0%
International Manpower	4,105	287	657	862	1,149	1,519	1,785	2,217	2,668	3,120	3,551	3,961	4,105
Clinical Grants	118,028	8,273	16,505	26,610	37,066	47,692	59,198	69,002	79,813	89,829	99,616	107,382	118,028
OA54 Services Purchased	100,707	9,075	18,150	26,418	35,160	43,412	50,319	58,571	66,823	74,936	83,653	92,370	100,707
Corporate Task	...	...	...	...	...	...	...	...	...	...	...	...	...
Judgment - Internal	6,060	5,668	8,576	10,520	11,809	14,098	18,823	17,258	14,205	12,070	12,669	11,287	6,060
Judgment - Published	(9,800)	(817)	(1,634)	(2,451)	(3,268)	(4,085)	(4,902)	(5,719)	(6,536)	(7,352)	(8,168)	(8,984)	(9,800)
Gabitril reimbursement from Commereic	...	...	...	...	...	...	...	...	...	...	...	...	...
Hand Post/Flash to Actual Adjustment	...	...	...	...	...	...	...	...	...	...	...	...	...
Other Project Changes:	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Gross PPD R&amp;D Expense</b>	<b>629,385</b>	<b>54,338</b>	<b>106,445</b>	<b>160,305</b>	<b>212,629</b>	<b>266,392</b>	<b>323,557</b>	<b>372,824</b>	<b>425,237</b>	<b>475,979</b>	<b>526,056</b>	<b>578,439</b>	<b>629,385</b>
OA55 Services Sold	(244,018)	(21,165)	(41,380)	(62,234)	(82,560)	(103,275)	(125,238)	(144,299)	(164,304)	(184,007)	(203,586)	(224,041)	(244,018)
<b>Net PPD R&amp;D Expense</b>	<b>385,367</b>	<b>33,173</b>	<b>65,065</b>	<b>98,071</b>	<b>130,069</b>	<b>163,117</b>	<b>198,319</b>	<b>228,525</b>	<b>260,933</b>	<b>291,972</b>	<b>322,470</b>	<b>354,398</b>	<b>385,367</b>

\* Do not report these lines for actuals; report only Total Pharmaceutical Discovery line. Detail is shown here for planning purposes only.

PPRD SERVICES PURCHASED  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Patents & Trademark	6,050	504	504	504	504	504	504	504	504	504	504	504	506	6,050
Corp Admin Fixed	5,445	454	454	454	454	454	454	454	454	454	454	454	451	5,445
Corp Cost Pools	5,070	423	423	423	423	423	423	423	423	423	423	423	417	5,070
Satellite Copy Charge	539	45	45	45	45	45	45	45	45	45	45	45	44	539
CHMD Services Purchased Fixed (AHD)	196	16	16	16	16	16	16	16	16	16	16	16	20	196
PPD Ops Fixed Allocations	3,232	269	269	269	269	269	269	269	269	269	269	269	273	3,232
CENG - Fixed Maintenance from PPD O	899	75	75	75	75	75	75	75	75	75	75	75	74	899
CHEN Variable (EWRS)	147	12	12	12	12	12	12	12	12	12	12	12	15	147
CMIS - Purchasing	747	62	62	62	62	62	62	62	62	62	62	62	65	747
CHMS Telecommunications	130	11	11	11	11	11	11	11	11	11	11	11	9	130
Fixed L C Exp - Admin. Services	421	35	35	35	35	35	35	35	35	35	35	35	36	421
Corp Eng EHS Fixed Allocation	597	50	50	50	50	50	50	50	50	50	50	50	47	597
<b>TOTAL CORPORATE ALLOCATION</b>	<b>23,473</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,956</b>	<b>1,957</b>	<b>23,473</b>
CMIS - Unit of Activity, Fixed - Other	2,667	222	222	222	222	222	222	222	222	222	222	222	225	2,667
CMIS - Unit of Activity, Fixed - Aegis	2,100	175	175	175	175	175	175	175	175	175	175	175	175	2,100
PPD Personnel D0A47	2,601	217	217	217	217	217	217	217	217	217	217	217	214	2,601
PPD Mfg Ops - Allocation	63	5	5	5	5	5	5	5	5	5	5	5	8	63
PPD Ops QA Inf Svcs/Reg Affairs	1,942	162	162	162	162	162	162	162	162	162	162	162	160	1,942
PPD Ops Returned Goods	136	11	11	11	11	11	11	11	11	11	11	11	15	136
Project Expense	7,099	592	592	592	592	592	592	592	592	592	592	592	587	7,099
<b>TOTAL BURDEN FILE</b>	<b>40,081</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,340</b>	<b>3,341</b>	<b>40,081</b>
SPD Pilot Plant Stack Card	24,497	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,035	24,497
SPD Bulk Direct (Chem/Ferm)	17,328	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	17,328
Excess Capacity Stack Card	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
Subtotal SPD (Other than TAP)	53,435	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,454	4,441	53,435
TAP Bulk Drug (D-TAP)	84	7	7	7	7	7	7	7	7	7	7	7	7	84
TAP - SPD Manpower & Bulk (D-453)	245	20	20	20	20	20	20	20	20	20	20	20	25	245
Pharmacogenetics - ADD Allocation	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Expense	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal (For Exp Cat)	329	27	27	27	27	27	27	27	27	27	27	27	32	329
Other Purchases:														
Clari Once-A-Day (Global AI Manpower)	7,763	973	973	973	973	483	483	483	483	483	483	483	487	7,763
Corp Drug User Fees	1,207	...	...	...	...	...	...	...	...	1,207	...	...	...	1,207
Patent to Operations (search services)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
D-A54 Floor Space (not in functionals)	182	15	15	15	15	15	15	15	15	15	15	15	17	182
D-A54 Deprec (not in functionals)	2,984	249	249	249	249	249	249	249	249	249	249	249	245	2,984
Molecular Probes	7	...	...	...	...	...	...	...	...	...	...	...	7	7
Inventory transfer for Protease 2nd Gen	...	...	...	...	...	...	...	...	...	...	...	...	...	...
SDG/Other	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Clinical Supplies (Tricia Geran -PPD Op	200	17	17	17	17	17	17	17	17	16	16	16	16	200
Aegis Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Library (D441) to CHMS	...	...	...	...	...	...	...	...	...	...	...	...	...	...
QA (D44N) to Operations	1,500	...	...	...	...	...	...	...	...	...	...	...	1,500	1,500
Sangstat (Cyclosporine)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Sangstat (Sangcya)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Gabitril Royalty	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Ritonavir/LaRoche Combo	...	...	...	...	...	...	...	...	...	...	...	...	...	...
NOVO Settlement	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Metabolex	...	...	...	...	...	...	...	...	...	...	...	...	...	...
FLAP/Vanguard	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Sanofi Cost Sharing w/Gabitril	...	...	...	...	...	...	...	...	...	...	...	...	...	...
CI charge from OPS (Clin Val Mgr) + \$4	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Triangle receipt \$2,935 +\$325 for1999	(5,381)	...	...	(807)	...	...	(1,345)	...	...	(1,345)	...	...	(1,884)	(5,381)
Comdisco	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Hydrocodone (IDV-in from HPD)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
CRO Rebates	(3,000)	...	...	...	(333)	(333)	(333)	(333)	(333)	(333)	(334)	(334)	(334)	(3,000)
Gabitril Reimbursement from Commerci	1,400	...	...	...	...	...	...	...	...	...	467	467	466	1,400
Other	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Grand Total</b>	<b>100,707</b>	<b>9,075</b>	<b>9,075</b>	<b>8,268</b>	<b>8,742</b>	<b>8,252</b>	<b>6,907</b>	<b>8,252</b>	<b>8,252</b>	<b>8,113</b>	<b>8,717</b>	<b>8,717</b>	<b>8,334</b>	<b>100,707</b>
(2,537)														



PPRD SERVICES PURCHASED  
RECONCILIATIONS YTD - \$  
2001 PLAN

02/19/01  
08:07 AM

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Patents & Trademark	6,050	504	1,008	1,512	2,016	2,520	3,024	3,528	4,032	4,536	5,040	5,544	6,050
Corp Admin Fixed	5,445	454	908	1,362	1,816	2,270	2,724	3,178	3,632	4,086	4,540	4,994	5,445
Corp Cost Pools	5,070	423	846	1,269	1,692	2,115	2,538	2,961	3,384	3,807	4,230	4,653	5,070
Satellite Copy Charge	539	45	90	135	180	225	270	315	360	405	450	495	539
CHMD Services Purchased Fixed (AHD)	196	16	32	48	64	80	96	112	128	144	160	176	196
PPD Ops Fixed Allocations	3,232	269	538	807	1,076	1,345	1,614	1,883	2,152	2,421	2,690	2,959	3,232
CENG - Fixed Maintenance from PPD O	899	75	150	225	300	375	450	525	600	675	750	825	899
CHEN Variable (EWRS)	147	12	24	36	48	60	72	84	96	108	120	132	147
CMIS - Purchasing	747	62	124	186	248	310	372	434	496	558	620	682	747
CHMS Telecommunications	130	11	22	33	44	55	66	77	88	99	110	121	130
Fixed L C Exp - Admin. Services	421	35	70	105	140	175	210	245	280	315	350	385	421
Corp Eng EHS Fixed Allocation	<u>597</u>	<u>50</u>	<u>100</u>	<u>150</u>	<u>200</u>	<u>250</u>	<u>300</u>	<u>350</u>	<u>400</u>	<u>450</u>	<u>500</u>	<u>550</u>	<u>597</u>
<b>TOTAL CORPORATE ALLOCATION</b>	<b>23,473</b>	<b>1,956</b>	<b>3,912</b>	<b>5,868</b>	<b>7,824</b>	<b>9,780</b>	<b>11,736</b>	<b>13,692</b>	<b>15,648</b>	<b>17,604</b>	<b>19,560</b>	<b>21,516</b>	<b>23,473</b>
CMIS - Unit of Activity, Fixed - Other	2,667	222	444	666	888	1,110	1,332	1,554	1,776	1,998	2,220	2,442	2,667
CMIS - Unit of Activity, Fixed - Aegis	2,100	175	350	525	700	875	1,050	1,225	1,400	1,575	1,750	1,925	2,100
PPD Personnel D0A47	2,601	217	434	651	868	1,085	1,302	1,519	1,736	1,953	2,170	2,387	2,601
PPD Mfg Ops - Allocation	63	5	10	15	20	25	30	35	40	45	50	55	63
PPD Ops QA Inf Svcs/Reg Affairs	1,942	162	324	486	648	810	972	1,134	1,296	1,458	1,620	1,782	1,942
PPD Ops Returned Goods	136	11	22	33	44	55	66	77	88	99	110	121	136
Project Expense	<u>7,099</u>	<u>592</u>	<u>1,184</u>	<u>1,776</u>	<u>2,368</u>	<u>2,960</u>	<u>3,552</u>	<u>4,144</u>	<u>4,736</u>	<u>5,328</u>	<u>5,920</u>	<u>6,512</u>	<u>7,099</u>
<b>TOTAL BURDEN FILE</b>	<b>40,081</b>	<b>3,340</b>	<b>6,680</b>	<b>10,020</b>	<b>13,360</b>	<b>16,700</b>	<b>20,040</b>	<b>23,380</b>	<b>26,720</b>	<b>30,060</b>	<b>33,400</b>	<b>36,740</b>	<b>40,081</b>
SPD Pilot Plant Stack Card	24,497	2,042	4,084	6,126	8,168	10,210	12,252	14,294	16,336	18,378	20,420	22,462	24,497
SPD Bulk Direct (Chem/Ferm)	17,328	1,444	2,888	4,332	5,776	7,220	8,664	10,108	11,552	12,996	14,440	15,884	17,328
Excess Capacity Stack Card	<u>11,610</u>	<u>968</u>	<u>1,936</u>	<u>2,904</u>	<u>3,872</u>	<u>4,840</u>	<u>5,808</u>	<u>6,776</u>	<u>7,744</u>	<u>8,712</u>	<u>9,680</u>	<u>10,648</u>	<u>11,610</u>
Subtotal SPD (Other than TAP)	53,435	4,454	8,908	13,362	17,816	22,270	26,724	31,178	35,632	40,086	44,540	48,994	53,435
TAP Bulk Drug (D-TAP)	84	7	14	21	28	35	42	49	56	63	70	77	84
TAP - SPD Manpower & Bulk (D-453)	245	20	40	60	80	100	120	140	160	180	200	220	245
Pharmacogenetics - ADD Allocation	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Expense	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal (For Exp Cat)	329	27	54	81	108	135	162	189	216	243	270	297	329
Other Purchases:	...	...	...	...	...	...	...	...	...	...	...	...	...
Clari Once-A-Day (Global AI Manpower)	7,763	973	1,947	2,920	3,893	4,876	5,849	6,822	7,795	8,768	9,741	10,714	11,687
Corp Drug User Fees	1,207	...	...	...	...	...	...	...	...	1,207	1,207	1,207	1,207
Patent to Operations (search services)	...	...	...	...	...	...	...	...	...	...	...	...	...
D-A54 Floor Space (not in functionals)	182	15	30	45	60	75	90	105	120	135	150	165	182
D-A54 Deprec (not in functionals)	2,984	249	498	747	996	1,245	1,494	1,743	1,992	2,241	2,490	2,739	2,984
Molecular Probes	7	...	...	...	...	...	...	...	...	...	...	...	7
Inventory transfer for Protease 2nd Gen	...	...	...	...	...	...	...	...	...	...	...	...	...
SDG/Other	...	...	...	...	...	...	...	...	...	...	...	...	...
Clinical Supplies (Tricia Geran - PPD Op	200	17	34	51	68	85	102	119	136	152	168	184	200
Aegis Charges	...	...	...	...	...	...	...	...	...	...	...	...	...
Library (D441) to CHMS	...	...	...	...	...	...	...	...	...	...	...	...	...
QA (D44N) to Operations	1,500	...	...	...	...	...	...	...	...	...	...	...	1,500
Sangstat (Cyclosporine)	...	...	...	...	...	...	...	...	...	...	...	...	...
Sangstat (Sangcya)	...	...	...	...	...	...	...	...	...	...	...	...	...
Gabitril Royalty	...	...	...	...	...	...	...	...	...	...	...	...	...
Ritonavir/LaRoche Combo	...	...	...	...	...	...	...	...	...	...	...	...	...
NOVO Settlement	...	...	...	...	...	...	...	...	...	...	...	...	...
Metabolex	...	...	...	...	...	...	...	...	...	...	...	...	...
FLAP/Vanguard	...	...	...	...	...	...	...	...	...	...	...	...	...
Sanofi Cost Sharing w/Gabitril	...	...	...	...	...	...	...	...	...	...	...	...	...
CI charge from OPS (Clin Val Mgr) + \$4	...	...	...	...	...	...	...	...	...	...	...	...	...
Triangle receipt \$2,935 + \$325 for 1999	(5,381)	...	...	(807)	(807)	(807)	(2,152)	(2,152)	(2,152)	(3,497)	(3,497)	(3,497)	(5,381)
Comdisco	...	...	...	...	...	...	...	...	...	...	...	...	...
Hydrocodone (IDV-in from HPD)	...	...	...	...	...	...	...	...	...	...	...	...	...
CRO Rebates	(3,000)	...	...	...	(333)	(666)	(999)	(1,332)	(1,665)	(1,998)	(2,332)	(2,666)	(3,000)
Gabitril Reimbursement from Commerci	1,400	...	...	...	...	...	...	...	...	...	467	934	1,400
Other	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Grand Total</b>	<b>100,707</b>	<b>9,075</b>	<b>18,151</b>	<b>26,419</b>	<b>35,161</b>	<b>43,413</b>	<b>50,321</b>	<b>58,573</b>	<b>66,825</b>	<b>74,938</b>	<b>83,656</b>	<b>92,373</b>	<b>100,707</b>

HIGHLY

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ADRT 0037521

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PPRD SERVICES SOLD  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
08:07 AM

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
% RATE - ACTUALS														
% RATE - MONTHLY PROJECTION		...	...	...	...	...	...	...	...	...	...	...	...	...
Cumulative % Rate		...	...	...	...	...	...	...	...	...	...	...	...	...
% RATE - ADJUSTED PROJECTION														
<b>AI GLOBAL PHARMACEUTICAL</b>	<b>186,670</b>	<b>16,385</b>	<b>15,435</b>	<b>16,074</b>	<b>15,546</b>	<b>15,935</b>	<b>17,183</b>	<b>14,280</b>	<b>15,224</b>	<b>14,922</b>	<b>14,798</b>	<b>15,674</b>	<b>15,214</b>	<b>186,670</b>
Direct Sister Benefit														
R&D Scientific Service (fixed)	2,384	199	199	199	199	199	199	199	199	199	199	199	195	2,384
Direct Service	3,800	317	317	317	317	317	317	317	317	317	317	317	313	3,800
Total Direct Sister Benefit	6,184	516	516	516	516	516	516	516	516	516	516	516	508	6,184
<b>Total Intl Sister Division</b>	<b>192,854</b>	<b>16,901</b>	<b>15,951</b>	<b>16,590</b>	<b>16,062</b>	<b>16,451</b>	<b>17,699</b>	<b>14,796</b>	<b>15,740</b>	<b>15,438</b>	<b>15,314</b>	<b>16,190</b>	<b>15,722</b>	<b>192,854</b>
TAP - SPD Manpower	245	20	20	20	20	20	20	20	20	20	20	20	25	245
TAP - Judgment (Positive Controls)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
TAP - Bulk Drug	84	7	7	7	7	7	7	7	7	7	7	7	7	84
TAP - All Other	19,856	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,655	1,651	19,856
<b>Total TAP</b>	<b>20,185</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,682</b>	<b>1,683</b>	<b>20,185</b>
Domestic Sister Divisions														
HPD	8,834	736	736	736	736	736	736	736	736	736	736	736	738	8,834
ADD	2,383	199	199	199	199	199	199	199	199	199	199	199	194	2,383
SPD	4,909	409	409	409	409	409	409	409	409	409	409	409	410	4,909
ROSS	1,955	163	163	163	163	163	163	163	163	163	163	163	162	1,955
CPD	42	4	4	4	4	4	4	4	4	4	4	4	(2)	42
MIS	74	6	6	6	6	6	6	6	6	6	6	6	8	74
AHD (AHS Abbott Health Systems)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
CHMS Library Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Corp Eng	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Total Domestic Sister Division</b>	<b>18,197</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,517</b>	<b>1,510</b>	<b>18,197</b>
Other Sister Divisions:														
Corp Administration														
Corp. Admin.	24	2	2	2	2	2	2	2	2	2	2	2	2	24
TAP Rate Diff (Fixed)	485	40	40	40	40	40	40	40	40	40	40	40	45	485
Symposium Expense (Fixed)	165	14	14	14	14	14	14	14	14	14	14	14	11	165
<b>Subtotal CHAD</b>	<b>674</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>56</b>	<b>58</b>	<b>674</b>
PPD Product R&D														
Mfg Support (MC,PM)	12,215	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,018	1,017	12,215
Mfg Support (PV)	263	22	22	22	22	22	22	22	22	22	22	22	21	263
PPD Marketing (P5,P6) (Inc Cephalon)	3,620	302	302	302	302	302	302	302	302	302	302	302	298	3,620
<b>Subtotal Other</b>	<b>16,098</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,342</b>	<b>1,336</b>	<b>16,098</b>
VAT Refund	...	...	...	...	...	...	...	...	...	...	...	...	...	...
PARD Services Sold Impact (Judgeme Rounding)	(3,990)	(333)	(333)	(333)	(333)	(333)	(333)	(332)	(332)	(332)	(332)	(332)	(332)	(3,990)
<b>GRAND TOTAL</b>	<b>244,018</b>	<b>21,165</b>	<b>20,215</b>	<b>20,854</b>	<b>20,326</b>	<b>20,715</b>	<b>21,963</b>	<b>19,061</b>	<b>20,005</b>	<b>19,703</b>	<b>19,579</b>	<b>20,455</b>	<b>19,977</b>	<b>244,018</b>
Memo: Excluding Global - \$		4,780	4,780	4,780	4,780	4,780	4,780	4,781	4,781	4,781	4,781	4,781	4,763	57,348
Quarterly - \$				14,340			14,340			14,343			14,325	57,348
Excluding Global - % of Qtr				25.0%			25.0%			25.0%			25.0%	
Excluding Global - % Dec													8.3%	

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PPRD SERVICES SOLD  
RECONCILIATIONS YTD - \$  
2001 PLAN02/19/01  
08:07 AM

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
AI GLOBAL PHARMACEUTICAL	186,670	16,385	31,820	47,894	63,440	79,375	96,558	110,838	126,062	140,984	155,782	171,456	186,670
Direct Sister Benefit													
R&D Scientific Service (fixed):	2,384	199	398	597	796	995	1,194	1,393	1,592	1,791	1,990	2,189	2,384
Direct Service	3,800	317	634	951	1,268	1,585	1,902	2,219	2,536	2,853	3,170	3,487	3,800
Total Direct Sister Benefit	6,184	516	1,032	1,548	2,064	2,580	3,096	3,612	4,128	4,644	5,160	5,676	6,184
Total Int'l Sister Division	192,854	16,901	32,852	49,442	65,504	81,955	99,654	114,450	130,190	145,628	160,942	177,132	192,854
TAP - SPD Manpower	245	20	40	60	80	100	120	140	160	180	200	220	245
TAP - Judgment	---	---	---	---	---	---	---	---	---	---	---	---	---
TAP - Bulk	84	7	14	21	28	35	42	49	56	63	70	77	84
TAP - All Other	19,856	1,655	3,310	4,965	6,620	8,275	9,930	11,585	13,240	14,895	16,550	18,205	19,856
Total TAP	20,185	1,682	3,364	5,046	6,728	8,410	10,092	11,774	13,456	15,138	16,820	18,502	20,185
Domestic Sister Divisions													
HPD	8,834	736	1,472	2,208	2,944	3,680	4,416	5,152	5,888	6,624	7,360	8,096	8,834
ADD	2,383	199	398	597	796	995	1,194	1,393	1,592	1,791	1,990	2,189	2,383
SPD	4,909	409	818	1,227	1,636	2,045	2,454	2,863	3,272	3,681	4,090	4,499	4,909
ROSS	1,955	163	326	489	652	815	978	1,141	1,304	1,467	1,630	1,793	1,955
CPD	42	4	8	12	16	20	24	28	32	36	40	44	42
MIS	74	6	12	18	24	30	36	42	48	54	60	66	74
AHD (AHS Abbott Health Systems)	---	---	---	---	---	---	---	---	---	---	---	---	---
CHMS Library Charges	---	---	---	---	---	---	---	---	---	---	---	---	---
Corp Eng	---	---	---	---	---	---	---	---	---	---	---	---	---
Total Domestic Sister Division	18,197	1,517	3,034	4,551	6,068	7,585	9,102	10,619	12,136	13,653	15,170	16,687	18,197
Other Sister Divisions:													
Corp Administration													
Corp. Admin.	24	2	4	6	8	10	12	14	16	18	20	22	24
TAP Rate Diff	485	40	80	120	160	200	240	280	320	360	400	440	485
Symposium Expense	165	14	28	42	56	70	84	98	112	126	140	154	165
Subtotal CHAD	674	56	112	168	224	280	336	392	448	504	560	616	674
PPD Product R&D													
Mfg Support (MC,PM)	12,215	1,018	2,036	3,054	4,072	5,090	6,108	7,126	8,144	9,162	10,180	11,198	12,215
Mfg Support (PV)	263	22	44	66	88	110	132	154	176	198	220	242	263
PPD Marketing (P5,P6) (Inc Cephalon)	3,620	302	604	906	1,208	1,510	1,812	2,114	2,416	2,718	3,020	3,322	3,620
Subtotal Other	16,098	1,342	2,684	4,026	5,368	6,710	8,052	9,394	10,736	12,078	13,420	14,762	16,098
VAT Refund	---	---	---	---	---	---	---	---	---	---	---	---	---
PARD Services Sold Impact (Judgeme	(3,990)	(333)	(666)	(999)	(1,332)	(1,665)	(1,998)	(2,330)	(2,662)	(2,994)	(3,326)	(3,658)	(3,990)
Rounding	---	---	---	---	---	---	---	---	---	---	---	---	---
GRAND TOTAL	244,018	21,165	41,380	62,234	82,560	103,275	125,238	144,299	164,304	184,007	203,586	224,041	244,018

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PPRD CLINICAL GRANTS  
RECONCILIATIONS MONTH - \$  
2001 PLAN02/18/01  
08:07 AM

	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	DEC ADJ	TOTAL
<b>PPD SERVICE :</b>															
Tiagabine/Gabitril	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Omnicel	3,000	---	---	---	---	---	---	---	600	600	600	600	600	---	3,000
Depakote/Depakene	9,441	723	(88)	1,179	1,180	1,180	1,180	1,180	1,181	608	373	373	372	---	9,441
r-Pro-UK	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Fenofibrate (Fournier)	39	39	---	---	---	---	---	---	---	---	---	---	---	---	39
Hematin	600	---	120	120	120	120	120	---	---	---	---	---	---	---	600
PharmacoGenetics (Genet)	200	---	---	20	20	20	20	20	20	20	20	20	20	---	200
<b>TOTAL PPD SERVICE</b>	<b>13,280</b>	<b>762</b>	<b>32</b>	<b>1,319</b>	<b>1,320</b>	<b>1,320</b>	<b>1,320</b>	<b>1,200</b>	<b>1,801</b>	<b>1,228</b>	<b>993</b>	<b>993</b>	<b>992</b>	<b>---</b>	<b>13,280</b>
<b>GLOBAL SERVICE :</b>															
Ritonavir ABT-538	1,244	299	(142)	109	109	109	109	109	109	109	108	108	108	---	1,244
Protease 2nd Gen ABT-378	22,575	120	1,818	1,892	2,001	2,243	2,239	2,166	2,155	1,953	1,996	1,996	1,996	---	22,575
Dopamine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
KCO ABT-598	380	---	---	---	---	---	---	---	---	---	---	190	190	---	380
ABT-594 (formerly CCM)	1,065	100	30	101	120	120	120	120	120	120	48	48	18	---	1,065
ABT-089 (formerly ChCM)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Clarithromycin	2,940	172	172	260	260	260	260	260	260	259	259	259	259	---	2,940
Ketolide ABT-773	47,405	4,847	4,847	4,925	4,960	4,960	4,960	3,403	3,403	3,386	323	3,695	3,696	---	47,405
Prokinetic Macrolide - Dom	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Zileuton & 2nd Generation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
BPH ABT-980	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cyclosporine	993	464	35	125	115	115	35	35	35	34	---	---	---	---	993
H2G (Medivir)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Endothelin	19,251	1,035	1,035	1,035	1,035	1,035	1,849	1,897	1,897	1,897	2,179	2,179	2,178	---	19,251
NS 49 Nippon Shinyaku ABT-23	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Bimoclomol (Biorex)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Anti-Mitotic ABT-751	1,025	---	---	---	75	75	125	125	125	125	125	125	125	---	1,025
Hytrin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
FTI (Farnesyltransferase)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
MMPi (Metalloprotease)	1,118	64	64	64	64	64	114	114	114	114	114	114	114	---	1,118
Taxane	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
TSP Peptide	1,621	116	116	116	88	116	166	166	166	165	165	165	76	---	1,621
Quinolone	5,000	229	159	159	309	209	209	209	626	626	477	894	894	---	5,000
Cox II	131	65	66	---	---	---	---	---	---	---	---	---	---	---	131
Neuraminidase	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Adjustment (EVR)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
<b>TOTAL GLOBAL SERVICE</b>	<b>104,748</b>	<b>7,511</b>	<b>8,200</b>	<b>8,786</b>	<b>9,136</b>	<b>9,306</b>	<b>10,186</b>	<b>8,604</b>	<b>9,010</b>	<b>8,788</b>	<b>5,794</b>	<b>5,773</b>	<b>9,654</b>	<b>---</b>	<b>104,748</b>
<b>MISC:</b>															
Vitamin D Analog/Iron Dextran	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Isotretinoin/Norvir Investigation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Adjustments	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Desmedetomidine/Zamplar (HPD)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Traxene Reformulation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Blaxin Reformulation	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
<b>GRAND TOTAL GRANTS</b>	<b>118,028</b>	<b>8,273</b>	<b>8,232</b>	<b>10,105</b>	<b>10,456</b>	<b>10,626</b>	<b>11,506</b>	<b>9,804</b>	<b>10,811</b>	<b>10,016</b>	<b>6,787</b>	<b>10,766</b>	<b>10,646</b>	<b>---</b>	<b>118,028</b>
- Quarterly Percentages				22.5%			27.6%			26.0%		23.9%			100.0%
Actuals							11,506								
Total Global Grants	104,748	7,511	8,200	8,786	9,136	9,306	10,186	8,604	9,010	8,788	5,794	5,773	9,654	---	104,748
Total Other Domestic Grants	13,280	762	32	1,319	1,320	1,320	1,200	1,801	1,228	993	993	992	---	---	13,280
Total Other Grants	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Total Grants	118,028	8,273	8,232	10,105	10,456	10,626	11,506	9,804	10,811	10,016	6,787	10,766	10,646	---	118,028
Key Checks (sub O)															
Grant System (Excel as of 1/27/01)	118,028	8,273	8,232	10,105	10,456	10,626	11,506	9,804	10,811	10,016	6,787	10,766	10,646	---	118,028
Difference	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

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PPRD CLINICAL GRANTS  
RECONCILIATIONS - YTD \$  
2001 PLAN02/19/01  
08:27 AM

	01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
<b>PPD SERVICE :</b>													
Tiagabine/Gabitril	...	...	...	...	...	...	...	...	...	...	...	...	...
Omnicel	3,000	...	...	...	...	...	...	...	600	1,200	1,800	2,400	3,000
Depakote/Depakene	9,441	723	635	1,814	2,994	4,174	5,354	6,534	7,715	8,323	8,696	9,069	9,441
r-Pro-UK	...	...	...	...	...	...	...	...	...	...	...	...	...
Fenofibrate (Fournier)	39	39	39	39	39	39	39	39	39	39	39	39	39
Hematin	600	...	120	240	360	480	600	600	600	600	600	600	600
PharmacoGenetics (Genset)	200	...	...	20	40	60	80	100	120	140	160	180	200
<b>TOTAL PPD SERVICE</b>	<b>13,280</b>	<b>762</b>	<b>794</b>	<b>2,113</b>	<b>3,433</b>	<b>4,753</b>	<b>6,073</b>	<b>7,273</b>	<b>9,074</b>	<b>10,302</b>	<b>11,295</b>	<b>12,288</b>	<b>13,280</b>
<b>GLOBAL SERVICE :</b>													
Ritonavir ABT-538	1,244	299	157	266	375	484	593	702	811	920	1,028	1,136	1,244
Protease 2nd Gen ABT-378	22,575	120	1,938	3,830	5,831	8,074	10,313	12,479	14,634	16,587	18,583	20,579	22,575
Dopamine	...	...	...	...	...	...	...	...	...	...	...	...	...
KCO ABT-598	380	...	...	...	...	...	...	...	...	...	...	190	380
ABT-594 (formerly CCM)	1,065	100	130	231	351	471	591	711	831	951	999	1,047	1,065
ABT-089 (formerly ChCM)	...	...	...	...	...	...	...	...	...	...	...	...	...
Clarithromycin	2,940	172	344	604	864	1,124	1,384	1,644	1,904	2,163	2,422	2,681	2,940
Ketolide ABT-773	47,405	4,847	9,694	14,619	19,579	24,539	29,499	32,902	36,305	39,691	40,014	43,709	47,405
Prokinetic Macrolide - Dom	...	...	...	...	...	...	...	...	...	...	...	...	...
Zileuton & 2nd Generation	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH ABT-980	...	...	...	...	...	...	...	...	...	...	...	...	...
Cyclosporine	993	464	499	624	739	854	889	924	959	993	993	993	993
H2G (Medivir)	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	19,251	1,035	2,070	3,105	4,140	5,175	7,024	8,921	10,818	12,715	14,894	17,073	19,251
MS 49 Nippon Shinyaku ABT-23	...	...	...	...	...	...	...	...	...	...	...	...	...
Bimoclomol (Biores)	...	...	...	...	...	...	...	...	...	...	...	...	...
Anti-Mitotic ABT-751	1,025	...	...	...	75	150	275	400	525	650	775	900	1,025
Hytrin	...	...	...	...	...	...	...	...	...	...	...	...	...
MMP1 (Metalloprotease)	1,118	64	128	192	256	320	434	548	662	776	890	1,004	1,118
Taxane	...	...	...	...	...	...	...	...	...	...	...	...	...
TSP Peptide	1,621	116	232	348	436	552	718	884	1,050	1,215	1,380	1,545	1,621
Quinolone	5,000	229	388	547	856	1,065	1,274	1,483	2,109	2,735	3,212	4,106	5,000
Cox II	131	65	131	131	131	131	131	131	131	131	131	131	131
Neuraminidase	...	...	...	...	...	...	...	...	...	...	...	...	...
Adjustment (EVR)	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>TOTAL GLOBAL SERVICE</b>	<b>104,748</b>	<b>7,511</b>	<b>15,711</b>	<b>24,497</b>	<b>33,633</b>	<b>42,939</b>	<b>53,125</b>	<b>61,729</b>	<b>70,739</b>	<b>79,527</b>	<b>85,321</b>	<b>95,094</b>	<b>104,748</b>
Vitamin D Analog/Iron Dextran	...	...	...	...	...	...	...	...	...	...	...	...	...
Isotretinoin/Norvir Investigation	...	...	...	...	...	...	...	...	...	...	...	...	...
Adjustments	...	...	...	...	...	...	...	...	...	...	...	...	...
Doxmedetomidine/Zemplar (HPD)	...	...	...	...	...	...	...	...	...	...	...	...	...
Tranxene Reformulation	...	...	...	...	...	...	...	...	...	...	...	...	...
Biaxin Reformulation	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>GRAND TOTAL GRANTS</b>	<b>118,028</b>	<b>8,273</b>	<b>16,505</b>	<b>26,610</b>	<b>37,066</b>	<b>47,692</b>	<b>59,198</b>	<b>69,002</b>	<b>79,813</b>	<b>89,829</b>	<b>96,616</b>	<b>107,382</b>	<b>118,028</b>

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Pharmaceutical Products Research & Development  
Grants System  
2001 PLAN Galting

Rec.#	Protocol #	Study Description	Project Name	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Pts	Total Nts	# of Nts	1/100	Start	End
-New study																					
M88-132	070601	SC, FLA BIOAVAIL CLINIC	RITONAVIR SEMI-SOLID ARTESIN	44	(84)	38	38	38	38	38	38	38	38	38	38	...	286	6	44	Nov-98	Apr-00
M88-132	070601	SC, FLA BIOAVAIL CLINIC	RITONAVIR SEMI-SOLID ARTESIN	44	(84)	38	38	38	38	38	38	38	38	38	38	340	1,449	33	44	Jan-99	Mar-02
M88-215	070566	INATE & CO-STANCE PHARM ERUC-A	RITONAVIR SEMI-SOLID ARTESIN	45	(87)	42	42	42	42	42	42	42	42	42	42	380	1,485	33	44	Jan-99	Mar-02
M88-215	070566	INATE & CO-STANCE PHARM ERUC-A	RITONAVIR SEMI-SOLID ARTESIN	45	(87)	42	42	42	42	42	42	42	42	42	42	380	1,485	33	44	Jan-99	Mar-02
M88-047	070644	VARIUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	177	200	1	200	Jan-01	Jan-01
M88-047	070644	PROMETHEUS	RITONAVIR SEMI-SOLID ARTESIN	177	...	...	...	...	...	...	...	...	...	...	...	17					

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Pharmaceutical Products Research & Development  
Genetics System  
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Row #	Product	Study Description	Project Name	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Plan	Total Res	# of Mo	Start	End
107635	MSP-813	MULTI-CENTER	CYCLOSPORINE NEORAL-LIKE	35	35	35	35	35	35	35	35	34	...	...	...	...	1,712	16	107 3/89	8/00
107636	MSP-033	MULTI-CENTER	CYCLOSPORINE NEORAL-LIKE	...	...	...	...	...	...	...	...	...	...	...	...	...	1,040	10	104 8/89	8/00
107637	N/A	LAS PHARMACOLOGICAL RES	CYCLOSPORINE NEORAL-LIKE	...	...	...	...	...	...	...	...	...	...	...	...	...	850	6	142 10/89	3/00
107638	MSP-041	MULTI-CENTER CYCLOSPORINE	CYCLOSPORINE NEORAL-LIKE	...	...	...	...	...	...	...	...	...	...	...	...	...	815	22	37 12/89	9/01
107639	TBD	ASBOTT/BIOMATAT GENORAF STUDY	CYCLO PHASE IV	419	...	...	...	...	...	...	...	...	...	...	...	...	250	...	#DIV/0! Mar-01	Jan-01
107640	MSP-133	ASBOTT/BIOMATAT GENORAF STUDY	CYCLO PHASE IV	419	...	...	...	...	...	...	...	...	...	...	...	...	6,000	...	#DIV/0! Jul-00	Jan-01
107637	MSP-006	RENDLEAU-GENE	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	380	10	38 Apr-89	Jan-00
107638	MSP-084	RENDLEAU-GENE	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	3,500	1	...	Dec-89
107639	MSP-085	RENDLEAU-GENE	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	7,400	28	271 Dec-89	Mar-02
107640	MSP-086	RENDLEAU-GENE	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	224	6	45 Mar-00	Jul-00
107641	MSP-146	BIO-KINETIC CLINICAL APPL	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	950	(7)	(138) Mar-01	Jul-00
107642	MSP-131	RADIANT RESEARCH	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	3,800	12	317 Mar-00	Feb-01
107643	MSP-098	PRO DEVELOPMENT	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	3,800	12	317 Mar-00	Feb-01
107644	MSP-097	PRO DEVELOPMENT	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	1,400	6	81 Mar-00	Aug-01
107645	MSP-099	Qu's Drug Research Unit	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	850	14	81 Mar-00	Aug-01
107646	MSP-166	MULTI-CENTER TRIAL	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	210	11	19 Jul-00	Mar-01
107647	MSP-172	CLINICAL RESEARCH SERVICE	SPH ARTS80	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
107648	MSP-114	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	3,100	12	288 Feb-00	Jan-01
107649	MSP-115	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,181	3	18 Mar-01	Dec-01
107650	MSP-116	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107651	MSP-117	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107652	MSP-118	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107653	MSP-119	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107654	MSP-120	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107655	MSP-121	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107656	MSP-122	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107657	MSP-123	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107658	MSP-124	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107659	MSP-125	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107660	MSP-126	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107661	MSP-127	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107662	MSP-128	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107663	MSP-129	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107664	MSP-130	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107665	MSP-131	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107666	MSP-132	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107667	MSP-133	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107668	MSP-134	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107669	MSP-135	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107670	MSP-136	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107671	MSP-137	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107672	MSP-138	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107673	MSP-139	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107674	MSP-140	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107675	MSP-141	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107676	MSP-142	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107677	MSP-143	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107678	MSP-144	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107679	MSP-145	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107680	MSP-146	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107681	MSP-147	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107682	MSP-148	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107683	MSP-149	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107684	MSP-150	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107685	MSP-151	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107686	MSP-152	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107687	MSP-153	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107688	MSP-154	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107689	MSP-155	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107690	MSP-156	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107691	MSP-157	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107692	MSP-158	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107693	MSP-159	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107694	MSP-160	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107695	MSP-161	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107696	MSP-162	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107697	MSP-163	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107698	MSP-164	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107699	MSP-165	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107700	MSP-166	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107701	MSP-167	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107702	MSP-168	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...	...	1,500	10	30 Jan-01	Nov-01
107703	MSP-169	Neuroleptic Pan	ARTS84	100	...	...	...	...	...	...	...	...	...	...	...					



Pharmaceutical Products Research & Development  
Grants System  
2001 PLAN Gating

Pharmaceutical Products Research & Development Grants System 2001 PLAN Gating																				
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Res #	Project Name	Study Description	Fenofibrate	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Pen	Total Res	# of Mo	Start	End
107591	N/A	POST-MENOPAUSAL WOMEN	Fenofibrate	39												39		1	Jan-00	Jan-00
Notes																				
107495	MDS-820 NEW	Baron & Polinsky Asset And-Herses		8,221	8,221	10,104	10,418	10,428	11,805	8,802	10,808	10,012	8,718	10,814	10,814	118,922	2,359	24	08/01/99	01/01/00
Grand Total																				
				6,778	6,681	7,148	7,879	7,720	8,431	7,088	8,092	8,101	8,140	8,130	8,088	91,380				
NEW				1,488	1,351	2,538	2,877	2,508	2,874	2,718	2,717	1,816	1,848	1,847	1,882	26,447				
Grand Total Less New																				

## NOTES

- When a fee number changes from New (blue) to a number, it indicates to update the fee amount as well as the start and end date to match the new number.
- This worksheet should only contain numbers in the system. Actuals are to date, the other numbers are projected in the system.

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PPRD GREYBOOK  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
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	GLOBAL													
CHARGES TO PROJECTS:	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<i>Memo: Global Key Check</i>														
Global	466,675	40,963	38,588	40,185	38,865	39,837	42,958	35,700	38,060	37,305	36,995	39,185	38,034	466,675
Direct Service														
PPD Service	105,362	8,262	8,406	8,562	8,346	8,813	9,094	8,454	9,240	8,324	7,969	8,085	11,807	105,362
Sister & Takeda	57,348	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	5,113	1,105	57,348
<b>TOTAL GROSS EXPENSE</b>	<b>629,385</b>	<b>54,338</b>	<b>52,107</b>	<b>53,860</b>	<b>52,324</b>	<b>53,763</b>	<b>57,165</b>	<b>49,267</b>	<b>52,413</b>	<b>50,742</b>	<b>50,077</b>	<b>52,383</b>	<b>50,946</b>	<b>629,385</b>
<b>LESS SISTER DIVISION CHARGES:</b>														
AI Total	192,854	16,901	15,951	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854
TAP Pharm, Inc.	20,185	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	1,682	20,185
HPD	8,834	736	736	736	736	736	736	736	736	736	736	736	736	8,834
ADD	2,383	199	199	199	199	199	199	199	199	199	199	199	199	2,383
SPD	4,909	409	409	409	409	409	409	409	409	409	409	409	410	4,909
ROSS	1,955	163	163	163	163	163	163	163	163	163	163	163	162	1,955
CPD	42	4	4	4	4	4	4	4	4	4	4	4	(2)	42
CMS	74	6	6	6	6	6	6	6	6	6	6	6	8	74
Other Sister Division	16,772	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,398	1,394	16,772
<b>TOTAL CHARGES OUT</b>	<b>248,008</b>	<b>21,498</b>	<b>20,548</b>	<b>21,187</b>	<b>20,659</b>	<b>21,048</b>	<b>22,296</b>	<b>19,393</b>	<b>20,337</b>	<b>20,035</b>	<b>19,911</b>	<b>20,787</b>	<b>20,309</b>	<b>248,008</b>
<b>PARD SERVICES SOLD IMPACT (Judgement)</b>	<b>3,990</b>	<b>333</b>	<b>333</b>	<b>333</b>	<b>333</b>	<b>333</b>	<b>333</b>	<b>332</b>	<b>332</b>	<b>332</b>	<b>332</b>	<b>332</b>	<b>332</b>	<b>3,990</b>
<b>NET PPRD EXPENSE</b>	<b>385,367</b>	<b>33,173</b>	<b>31,892</b>	<b>33,006</b>	<b>31,998</b>	<b>33,048</b>	<b>35,202</b>	<b>30,206</b>	<b>32,408</b>	<b>31,039</b>	<b>30,498</b>	<b>31,928</b>	<b>30,969</b>	<b>385,367</b>
ACTUALS PER GREYBOOK (J:DRIVE)														
VARIANCE/KEY CHECK	(33,173)	(31,892)	(33,006)	(31,998)	(33,048)	(35,202)	(30,206)	(32,408)	(31,039)	(30,498)	(31,928)	(30,969)	(385,367)	
ACTUALS PER KIRNES/DIANA														
VARIANCE/KEY CHECK	(33,173)	(31,892)	(33,006)	(31,998)	(33,048)	(35,202)	(30,206)	(32,408)	(31,039)	(30,498)	(31,928)	(30,969)	(385,367)	
<b>Memo: 2000 Actuals</b>	<b>32,133</b>	<b>30,404</b>	<b>35,911</b>	<b>33,138</b>	<b>32,058</b>	<b>45,704</b>	<b>28,013</b>	<b>27,124</b>	<b>29,386</b>	<b>27,095</b>	<b>27,115</b>	<b>27,512</b>	<b>375,593</b>	
<b>Memo:</b>														
AI 2001 PLAN (12/08/00)	16,901	15,951	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854	
AI Final 2000 AGU	10,645	14,364	14,799	14,474	16,424	17,281	17,969	15,360	19,401	19,301	16,441	15,581	192,040	
<b>Net PPRD Expense</b>														
	1Qtr	2Qtr	3Qtr	4Qtr	Total	2001 PLAN Fav/(Unfav) vs.								
2001 PLAN (12/08/00)	98,071	100,248	93,653	93,395	385,367	1Qtr	2Qtr	3Qtr	4Qtr	Total				
% of total	25.4%	26.0%	24.3%	24.2%	99.9%									
2000 Final AGU	98,448	110,900	84,906	80,476	374,730	377	10,652	(8,747)	(12,919)	(10,637)				
% of total	26.3%	29.6%	22.7%	21.5%	100.1%	0.4%	9.6%	-10.3%	-16.1%	-2.8%				
2000 Actuals	98,448	110,900	84,523	81,722	375,593	377	10,652	(9,130)	(11,673)	(9,774)				
% of total	26.2%	29.5%	22.5%	21.8%	100.0%	0.4%	9.6%	-10.8%	-14.3%	-2.6%				

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PPRD GREYBOOK  
RECONCILIATIONS YTD - \$  
2001 PLAN02/19/01  
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	GLOBAL												
CHARGES TO PROJECTS:	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC
Global	466,675	40,963	79,551	119,736	158,601	198,438	241,396	277,096	315,156	352,461	389,456	428,641	466,675
Direct Service													
PPD Service	105,362	8,262	16,668	25,230	33,576	42,389	51,483	59,937	69,177	77,501	85,470	93,555	105,362
Sister & Takeda	57,348	5,113	10,226	15,339	20,452	25,565	30,678	35,791	40,904	46,017	51,130	56,243	57,348
TOTAL GROSS EXPENSE	629,385	54,338	106,445	160,305	212,629	266,392	323,557	372,824	425,237	475,979	526,056	578,439	629,385
LESS SISTER DIVISION CHARGES:													
AI Total	192,854	16,901	32,852	49,442	65,504	81,955	99,654	114,450	130,190	145,628	160,942	177,132	192,854
TAP Pharm, Inc.	20,185	1,682	3,364	5,046	6,728	8,410	10,092	11,774	13,456	15,138	16,820	18,502	20,185
HPD	8,834	736	1,472	2,208	2,944	3,680	4,416	5,152	5,888	6,624	7,360	8,096	8,834
ADD	2,383	199	398	597	796	995	1,194	1,393	1,592	1,791	1,990	2,189	2,383
SPD	4,909	409	818	1,227	1,636	2,045	2,454	2,863	3,272	3,681	4,090	4,499	4,909
ROSS	1,955	163	326	489	652	815	978	1,141	1,304	1,467	1,630	1,793	1,955
CPD	42	4	8	12	16	20	24	28	32	36	40	44	42
CMIS	74	6	12	18	24	30	36	42	48	54	60	66	74
Other Sister Division	16,772	1,398	2,796	4,194	5,592	6,990	8,388	9,786	11,184	12,582	13,980	15,378	16,772
TOTAL CHARGES OUT	248,008	21,498	42,046	63,233	83,892	104,940	127,236	146,629	166,966	187,001	206,912	227,699	248,008
PARD SERVICES SOLD IMPACT (Judgement)	3,990	333	666	999	1,332	1,665	1,998	2,330	2,662	2,994	3,326	3,658	3,990
NET PPRD EXPENSE	385,367	33,173	65,065	98,071	130,069	163,117	198,319	228,525	260,933	291,972	322,470	354,398	385,367

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PPD RESEARCH AND DEVELOPMENT  
2001 PLAN  
P&L AI CALENDARIZATION

02/19/01  
08:07 AM

Modelling Factor: Input # months actuals in cell below													
0													
Modelling Calculations are in italics & pink high													
Modelling Factor: Input total Global \$'s in cell below													
466,675													
Global:													
Discovery Deals	0	625	2,015	250	625	2,015	250	625	2,015	250	625	3,151	12,446
Genset Payments	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0	0	0	0
Global Grants	7,511	8,200	8,786	9,136	9,306	10,186	8,604	9,010	8,788	5,794	9,773	9,654	104,748
Global SPD	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,916	47,069
Subtotal - Identified Global Expenses													
	11,434	12,748	14,724	13,309	13,854	16,124	12,777	13,558	14,726	9,967	14,321	16,721	164,263
All Other (see allocation basis at Memo 1)													
	28,321	26,804	25,267	25,086	25,904	26,801	23,555	24,836	23,141	26,028	24,689	21,980	302,412
Calculation of actuals													
	0	0	0	0	0	0	0	0	0	0	0	0	0
Calculation of remaining dollars													
													302,412
Total Global as Calculated													
	39,755	39,552	39,991	38,395	39,758	42,925	36,332	38,394	37,867	35,995	39,010	38,701	466,675
Adjust to Frozen AI Sellout	1,208	(964)	194	470	79	33	(632)	(334)	(562)	1,000	175	(667)	0
Freeze AI Sellout at these #'s - use actuals when av	40,963	38,588	40,185	38,865	39,837	42,958	35,700	38,060	37,305	36,995	39,185	38,034	466,675
Modelling Factor: If freezing AI sellout, input 1. If AI sellout can c													
1													
Total Global													
	40,963	38,588	40,185	38,865	39,837	42,958	35,700	38,060	37,305	36,995	39,185	38,034	466,675
Cumulative Global	40,963	79,551	119,736	158,601	198,438	241,396	277,096	315,156	352,461	389,456	428,641	466,675	466,675
Cumulative AI Share	(16,385)	(31,820)	(47,894)	(63,340)	(79,379)	(96,858)	(110,838)	(126,062)	(140,984)	(155,782)	(171,456)	(186,670)	(186,670)
Less AI Share	(16,385)	(15,435)	(16,074)	(15,546)	(15,935)	(17,183)	(14,280)	(15,224)	(14,922)	(14,798)	(15,674)	(15,214)	(186,670)
Domestic:													
Domestic Grants	762	32	1,319	1,320	1,320	1,320	1,200	1,801	1,228	993	993	992	(104,748)
Domestic SPD	531	531	531	531	531	531	531	531	531	531	531	525	6,366
Subtotal - Identified Domestic Expenses													
	1,293	563	1,850	1,851	1,851	1,851	1,731	2,332	1,759	1,524	1,524	1,517	(98,382)
All Other													
	7,302	8,176	7,045	6,828	7,295	7,576	7,055	7,240	6,897	6,777	6,893	6,632	85,716
Total Domestic													
	8,595	8,739	8,895	8,679	9,146	9,427	8,786	9,572	8,656	8,301	8,417	8,149	105,362
Memo 1:													
Total Net PPD R&D Expense													
	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Less 100% of Identified Domestic Exp (above)	(1,293)	(563)	(1,850)	(1,851)	(1,851)	(1,851)	(1,731)	(2,332)	(1,759)	(1,524)	(1,524)	(1,517)	(19,646)
Less 60% of Identified Global Exp (above)	(6,860)	(7,649)	(8,834)	(7,985)	(8,312)	(9,674)	(7,866)	(8,135)	(8,836)	(5,980)	(8,593)	(10,033)	(98,558)
All Other Not yet Calendarized (Allocation base)	25,020	23,680	22,322	22,162	22,885	23,677	20,809	21,941	20,444	22,994	21,811	19,418	267,163
Calculation of actuals													
	0	0	0	0	0	0	0	0	0	0	0	0	0
Calculation of remaining dollars													
	25,020	23,680	22,322	22,162	22,885	23,677	20,809	21,941	20,444	22,994	21,811	19,418	267,163
check figure must be zero before completed													
	0	0	0	0	0	0	0	0	0	0	0	0	0
Calculating preliminary calendarizations (for TRH review packages)													
1) Input actuals to detailed model. Confirm that net R&D ties to J drive (P&L&L&CAL WK4).													
2) Input items pulling into "Identified Global Expenses" and "Identified Domestic Expenses" above													
- From analysts: Discovery New Technology, Grants, SPD, License payments, refunds, etc.													
- We can guessimate Discovery functionals													
3) Input modelling factors above (# months actuals and total global \$'s)													
4) Make sure calendarization sheets (column B in Gated Grants, Func Expense, Svcs Purchased, Svcs Sold) are pulling correct annual # from Op Cost Stmt													
5) Model Quarterly Profile													
6) Model net R&D calendarization below. (Inputs are in blue.) Plug all other to achieve qtrly profile													
7) For APU preliminary estimates, March = Flash, April = Plan + Blue Plan impact													
For AGU preliminary estimates, July = Flash (if not available, use APU + BP), August = APU+ Blue Plan impact.													
8) Input Net R&D (as calculated below) to Func Expense Net Income sheet Line 87, on "This is input, judgment plugs to this #" line.													
Identified Global Expenses (Net)	6,860	7,649	8,834	7,985	8,312	9,674	7,666	8,135	8,836	5,980	8,593	10,033	98,557
Identified Domestic Expenses	1,293	563	1,850	1,851	1,851	1,851	1,731	2,332	1,759	1,524	1,524	1,517	19,646
Payroll	0	200	400	600	800	1,000	1,200	1,400	1,600	1,800	2,000	2,200	13,200
Adjustment for PLAN	0	0	0	0	0	0	0	0	0	0	0	0	0
TBD	0	0	0	0	0	0	0	0	0	0	0	0	0
TBD	0	0	0	0	0	0	0	0	0	0	0	0	0
Subtotal - Identified Net Expenses													
	8,153	8,412	11,084	10,436	10,963	12,525	10,597	11,867	12,195	9,304	12,117	13,750	131,403
All Other - see (a) for Actuals													
	25,020	23,480	21,922	21,562	22,085	22,677	19,609	20,541	18,844	21,194	19,811	17,219	253,964
Net R&D													
	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Calculation of actuals - Net R&D													
	0	0	0	0	0	0	0	0	0	0	0	0	0
Calculation of remaining dollars - Net R&D													
													385,367
(a) Calculation of actuals - All Other													
	0	0	0	0	0	0	0	0	0	0	0	0	0
Current Calendarization													
	33,173	31,892	33,006	31,998	33,048	35,202	30,206	32,408	31,039	30,498	31,928	30,969	385,367
Delta from line 80 above													
	0	0	0	0	0	0	0	0	0	0	0	0	0
2000 Final AGU													
	32,133	30,404	35,911	33,138	32,058	45,704	28,013	27,124	29,769	26,703	27,355	26,418	374,730
2000 Actuals													
	32,133	30,404	35,911	33,138	32,058	45,704	28,013	27,124	29,386	27,095	27,115	27,512	375,593
2001 Quarterly Profile													
2001 PLAN (12/08/00)													
	98,071	100,248	93,653	93,395	385,367								
Blue Plans													
	0	0	0	0	0								
Changes:													
	0	0	0	0	0								
TBD	0	0	0	0	0								
TBD	0	0	0	0	0								
Other (DIP)	0	0	0	0	0								
Total Expected PLAN													
	98,071	100,248	93,653	93,395	385,367								
Expected PLAN													
	0	0	0	0	0								

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PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT  
2001 PLAN  
GLOBAL AI CALENDARIZATION

02/19/01  
06:07 AM

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Global AI	16,385	15,435	16,074	15,546	15,935	17,183	14,280	15,224	14,922	14,798	15,674	15,214	186,670
Total Fixed AI	199	199	199	199	199	199	199	199	199	199	199	195	2,384
Total Direct AI	317	317	317	317	317	317	317	317	317	317	317	313	3,800
Total AI Support	516	516	516	516	516	516	516	516	516	516	516	508	6,184
Total Global	16,901	15,951	16,590	16,062	16,451	17,699	14,796	15,740	15,438	15,314	16,190	15,722	192,854
2000 AGU Global AI	10,645	14,364	14,799	14,474	16,424	17,281	17,969	15,360	19,401	19,301	16,441	15,581	192,040

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PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
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TOTAL FIXED AND DIRECT CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773)	14,970	1,248	1,248	1,248	1,248	1,248	1,248	1,248	1,248	1,248	1,248	1,248	1,242	14,970
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	683	57	57	57	57	57	57	57	57	57	57	57	56	683
NPS-1776	490	41	41	41	41	41	41	41	41	41	41	41	39	490
Quinolone	5,762	480	480	480	480	480	480	480	480	480	480	480	482	5,762
Cancer - Anti Mitotic (Eisai-7010)	1,172	98	98	98	98	98	98	98	98	98	98	98	94	1,172
Clari 140H	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	2,753	229	229	229	229	229	229	229	229	229	229	229	234	2,753
Clari IV	4,297	358	358	358	358	358	358	358	358	358	358	358	359	4,297
Clari Process Improvements	1,700	142	142	142	142	142	142	142	142	142	142	142	138	1,700
New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Process Impv (ery Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	31,827	2,653	2,653	2,653	2,653	2,653	2,653	2,653	2,653	2,653	2,653	2,653	2,644	31,827
<b>DISCOVERY</b>														
Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	370	31	31	31	31	31	31	31	31	31	31	31	29	370
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	2,621	218	218	218	218	218	218	218	218	218	218	218	223	2,621
Subtotal Discovery	2,991	249	249	249	249	249	249	249	249	249	249	249	252	2,991
<b>OTHER</b>														
Dom Other-Ery Proc Imp	369	31	31	31	31	31	31	31	31	31	31	31	28	369
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	23	2	2	2	2	2	2	2	2	2	2	2	1	23
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	5,390	449	449	449	449	449	449	449	449	449	449	449	451	5,390
New Projects	1,225	102	102	102	102	102	102	102	102	102	102	102	103	1,225
Excess Capacity	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,441</b>	<b>53,435</b>
				13,362			13,362			13,362			13,349	

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PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS YTD - \$  
2001 PLAN

02/19/01  
08:07 AM

TOTAL FIXED AND DIRECT CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	14,970	1,248	2,496	3,744	4,992	6,240	7,488	8,736	9,984	11,232	12,480	13,728	14,970	14,970
Macrolide (ABT 773)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	683	57	114	171	228	285	342	399	456	513	570	627	683	683
NPS-1776	490	41	82	123	164	205	246	287	328	369	410	451	490	490
Quinolone	5,762	480	960	1,440	1,920	2,400	2,880	3,360	3,840	4,320	4,800	5,280	5,762	5,762
Cancer - Anti Mitotic (Eisai-7010)	1,172	98	196	294	392	490	588	686	784	882	980	1,078	1,172	1,172
Clari 14OH	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	2,753	229	458	687	916	1,145	1,374	1,603	1,832	2,061	2,290	2,519	2,753	2,753
Clari IV	4,297	358	716	1,074	1,432	1,790	2,148	2,506	2,864	3,222	3,580	3,938	4,297	4,297
Clari Process Improvements	1,700	142	284	426	568	710	852	994	1,136	1,278	1,420	1,562	1,700	1,700
New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Process Impv (ery Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	31,827	2,653	5,306	7,959	10,612	13,265	15,918	18,571	21,224	23,877	26,530	29,183	31,827	31,827
<b>DISCOVERY</b>														
Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	370	31	62	93	124	155	186	217	248	279	310	341	370	370
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
Subtotal Discovery	2,991	249	498	747	996	1,245	1,494	1,743	1,992	2,241	2,490	2,739	2,991	2,991
<b>OTHER</b>														
Dom Other-Ery Proc Imp	369	31	62	93	124	155	186	217	248	279	310	341	369	369
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	23	2	4	6	8	10	12	14	16	18	20	22	23	23
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	5,390	449	898	1,347	1,796	2,245	2,694	3,143	3,592	4,041	4,490	4,939	5,390	5,390
New Projects	1,225	102	204	306	408	510	612	714	816	918	1,020	1,122	1,225	1,225
Excess Capacity	11,610	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>8,908</b>	<b>13,362</b>	<b>17,816</b>	<b>22,270</b>	<b>26,724</b>	<b>31,178</b>	<b>35,632</b>	<b>40,086</b>	<b>44,540</b>	<b>48,994</b>	<b>53,435</b>	<b>53,435</b>

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PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/18/01  
08:07 AM

FIXED CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773)	5,562	464	464	464	464	464	464	464	464	464	464	464	458	5,562
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	490	41	41	41	41	41	41	41	41	41	41	41	39	490
NPS-1776	490	41	41	41	41	41	41	41	41	41	41	41	39	490
Quinolone	3,362	280	280	280	280	280	280	280	280	280	280	280	282	3,362
Cancer - Anti Mitotic (Eisai-7010)	907	76	76	76	76	76	76	76	76	76	76	76	71	907
Clari 14OH	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	2,085	174	174	174	174	174	174	174	174	174	174	174	171	2,085
Clari IV	1,225	102	102	102	102	102	102	102	102	102	102	102	103	1,225
Clari Process Improvements	748	62	62	62	62	62	62	62	62	62	62	62	68	748
New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Process Impv (ary Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	14,869	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,240	1,229	14,869

**DISCOVERY**

Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	2,621	218	218	218	218	218	218	218	218	218	218	218	223	2,621
Subtotal Discovery	2,621	218	218	218	218	218	218	218	218	218	218	218	223	2,621

**OTHER**

Dom Other-Ery Proc Imp	369	31	31	31	31	31	31	31	31	31	31	31	28	369
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	23	2	2	2	2	2	2	2	2	2	2	2	1	23
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	5,390	449	449	449	449	449	449	449	449	449	449	449	451	5,390
New Projects	1,225	102	102	102	102	102	102	102	102	102	102	102	103	1,225
Excess Capacity	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...

Total SPD Fixed Charges 36,107 3,010 3,010 3,010 3,010 3,010 3,010 3,010 3,010 3,010 3,010 3,010 3,010 2,997 36,107

**DIRECT CHARGES**

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773)	9,408	784	784	784	784	784	784	784	784	784	784	784	784	9,408
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	193	16	16	16	16	16	16	16	16	16	16	16	17	193
NPS-1776	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinolone	2,400	200	200	200	200	200	200	200	200	200	200	200	200	2,400
Cancer - Anti Mitotic (Eisai-7010)	265	22	22	22	22	22	22	22	22	22	22	22	23	265
Clari 14OH	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	668	55	55	55	55	55	55	55	55	55	55	55	63	668
Clari IV	3,072	256	256	256	256	256	256	256	256	256	256	256	256	3,072
Clari Process Improvements	952	80	80	80	80	80	80	80	80	80	80	80	72	952
New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Process Impv (ary Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	16,958	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,413	1,415	16,958

**DISCOVERY**

Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	370	31	31	31	31	31	31	31	31	31	31	31	29	370
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Discovery	370	31	31	31	31	31	31	31	31	31	31	31	29	370

**OTHER**

Dom Other-Ery Proc Imp	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Excess Capacity	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...

Total SPD Direct Charges 17,328 1,444 1,444 1,444 1,444 1,444 1,444 1,444 1,444 1,444 1,444 1,444 1,444 17,328

PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS YTD - \$  
2001 PLAN02/19/01  
08:57 AM

FIXED CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773)	5,562	464	928	1,392	1,856	2,320	2,784	3,248	3,712	4,176	4,640	5,104	5,562	5,562
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	490	41	82	123	164	205	246	287	328	369	410	451	490	490
NPS-1776	490	41	82	123	164	205	246	287	328	369	410	451	490	490
Quinolone	3,362	280	560	840	1,120	1,400	1,680	1,960	2,240	2,520	2,800	3,080	3,362	3,362
Cancer - Anti Mitotic (Eisai-7010)	907	76	152	228	304	380	456	532	608	684	760	836	907	907
Clari 14OH	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	2,085	174	348	522	696	870	1,044	1,218	1,392	1,566	1,740	1,914	2,085	2,085
Clari IV	1,225	102	102	102	102	102	102	102	102	102	102	102	205	205
Clari Process Improvements	748	62	62	62	62	62	62	62	62	62	62	62	165	165
New Products	748	62	124	188	248	310	372	434	496	558	620	682	748	748
Misc Process Impv (ery Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	15,617	1,302	2,440	3,578	4,716	5,854	6,992	8,130	9,268	10,406	11,544	12,682	14,014	14,014
<b>DISCOVERY</b>														
Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
Subtotal Discovery	2,621	218	436	654	872	1,090	1,308	1,526	1,744	1,962	2,180	2,398	2,621	2,621
<b>OTHER</b>														
Dom Other-Ery Proc Imp	369	31	62	93	124	155	186	217	248	279	310	341	369	369
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	23	2	4	6	8	10	12	14	16	18	20	22	23	23
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	5,390	449	898	1,347	1,796	2,245	2,694	3,143	3,592	4,041	4,490	4,939	5,390	5,390
New Projects	1,225	102	204	306	408	510	612	714	816	918	1,020	1,122	1,225	1,225
Excess Capacity	11,610	969	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Total SPD Fixed Charges</b>	<b>36,855</b>	<b>3,072</b>	<b>5,980</b>	<b>8,888</b>	<b>11,796</b>	<b>14,704</b>	<b>17,612</b>	<b>20,520</b>	<b>23,428</b>	<b>26,336</b>	<b>29,244</b>	<b>32,152</b>	<b>35,252</b>	<b>35,252</b>

DIRECT CHARGES	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>PASS THROUGH CHARGES:</b>														
Protease 2nd Gen (ABT 378)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773)	9,408	784	1,568	2,352	3,136	3,920	4,704	5,488	6,272	7,056	7,840	8,624	9,408	9,408
Macrolide (ABT 773) Pediatric	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Macrolide (ABT 773) I.V.	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cholinergic Channel Modulator	...	...	...	...	...	...	...	...	...	...	...	...	...	...
BPH Backup	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Endothelin	193	16	32	48	64	80	96	112	128	144	160	176	193	193
NPS-1776	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinolone	2,400	200	400	600	800	1,000	1,200	1,400	1,600	1,800	2,000	2,200	2,400	2,400
Cancer - Anti Mitotic (Eisai-7010)	265	22	44	66	88	110	132	154	176	198	220	242	265	265
Clari 14OH	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Cancer - Angiogenesis	688	55	110	165	220	275	330	385	440	495	550	605	668	668
Clari IV	3,072	256	512	768	1,024	1,280	1,536	1,792	2,048	2,304	2,560	2,816	3,072	3,072
Clari Process Improvements	952	80	160	240	320	400	480	560	640	720	800	880	952	952
New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc Process Impv (ery Danisco)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Pass Through	16,958	1,413	2,826	4,239	5,652	7,065	8,478	9,891	11,304	12,717	14,130	15,543	16,958	16,958
<b>DISCOVERY</b>														
Natural Products Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Patents & Trademarks	370	31	62	93	124	155	186	217	248	279	310	341	370	370
Miscellaneous (Depr adjusted here)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Special Labs	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Subtotal Discovery	370	31	62	93	124	155	186	217	248	279	310	341	370	370
<b>OTHER</b>														
Dom Other-Ery Proc Imp	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari I	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Clari IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - ABT 378 IV	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc PMP	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other - Misc (Add'l Warehou	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Protease 2nd Gen to PPNC	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	...	...	...	...	...	...	...	...	...	...	...	...	...	...
New Projects	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Excess Capacity	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Unit of Activity Charges	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Global Other-Misc. MJH Adjust	...	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Total SPD Direct Charges</b>	<b>17,328</b>	<b>1,444</b>	<b>2,888</b>	<b>4,332</b>	<b>5,776</b>	<b>7,220</b>	<b>8,664</b>	<b>10,108</b>	<b>11,552</b>	<b>12,996</b>	<b>14,440</b>	<b>15,884</b>	<b>17,328</b>	<b>17,328</b>



PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
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	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>SUMMARY SPD</b>														
Total Pilot Plant/PMP Stack Card	24,497	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,042	2,035	24,497
Total Bulk Drug Direct	17,328	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	1,444	17,328
Total Excess Capacity Stack Card	11,610	968	968	968	968	968	968	968	968	968	968	968	962	11,610
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,441</b>	<b>53,435</b>
<b>SUMMARY GLOBAL/DOMESTIC</b>														
Total Global SPD	47,069	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,923	3,916	47,069
Total All Other Domestic SPD	6,366	531	531	531	531	531	531	531	531	531	531	531	525	6,366
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,454</b>	<b>4,441</b>	<b>53,435</b>

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KEY CHECK (S/B 0)-->

PPRD SERVICES PURCHASED - SPD  
RECONCILIATIONS YTD - \$  
2001 PLAN

	'01 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
<b>SUMMARY SPD</b>														
Total Pilot Plant/PMP Stack Card	24,497	2,042	4,084	6,126	8,168	10,210	12,252	14,294	16,336	18,378	20,420	22,462	24,497	24,497
Total Bulk Drug Direct	17,328	1,444	2,888	4,332	5,776	7,220	8,664	10,108	11,552	12,996	14,440	15,884	17,328	17,328
Total Excess Capacity Stack Card	11,610	968	1,936	2,904	3,872	4,840	5,808	6,776	7,744	8,712	9,680	10,648	11,610	11,610
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>8,908</b>	<b>13,362</b>	<b>17,816</b>	<b>22,270</b>	<b>26,724</b>	<b>31,178</b>	<b>35,632</b>	<b>40,086</b>	<b>44,540</b>	<b>48,994</b>	<b>53,435</b>	<b>53,435</b>
<b>SUMMARY GLOBAL/DOMESTIC</b>														
Total Global SPD	47,069	3,923	7,846	11,769	15,692	19,615	23,538	27,461	31,384	35,307	39,230	43,153	47,069	47,069
Total All Other Domestic SPD	6,366	531	1,062	1,593	2,124	2,655	3,186	3,717	4,248	4,779	5,310	5,841	6,366	6,366
<b>Total SPD</b>	<b>53,435</b>	<b>4,454</b>	<b>8,908</b>	<b>13,362</b>	<b>17,816</b>	<b>22,270</b>	<b>26,724</b>	<b>31,178</b>	<b>35,632</b>	<b>40,086</b>	<b>44,540</b>	<b>48,994</b>	<b>53,435</b>	<b>53,435</b>

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PPRD AFFORDABILITY  
RECONCILIATIONS MONTH - \$  
2001 PLAN

02/19/01  
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	2001 PLAN	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
SDG/Other	...	...	...	...	...	...	...	...	...	...	...	...	...	...
HIV/Knoll/QD/Other	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Aegis Insurance	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Genset #1	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Genset #2	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Neurosearch FTE \$2530, depr \$200	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Coactinon	...	...	...	...	...	...	...	...	...	...	...	...	...	...
SPD IDV Liponavir	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Thrombolytics to HPD (Ovrhd & Grants)	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Data Management Absorbition	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Other New Products	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinolone Payment	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Division Task	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Total SDG/Other	...	...	...	...	...	...	...	...	...	...	...	...	...	...

# ***Key Issues in 2001***

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**Pharmaceutical Research & Development  
Key Plus/Minus List  
2001  
(\$MM's)**

Description	Commentary	Probability	Fav/(Unfav)
DPI Agreement	Licensing agreement with Discovery Partners International. Accounting to be clarified with Corporate.	High	2.0
SPD Bulk drug for Ketolide	Discussions are currently on-going with SPD to drop the number of bulk manufacturing campaign runs from 5 to 4 for the April Update.	High	1.5 - 2.0
Kaletra FDA Strategy	The current Kaletra budget assumes all data that is scheduled to be submitted as part of the FDA Accelerated Approval timetable will be sufficient. In the event that the data is inconclusive (as determined by the FDA) additional dollars will be needed to continue existing studies.	High	(1.2)
Subtotal for High Probability Scenarios			2.3 - 2.8
CCM Milestone Funding	Go/No go decision is scheduled for May/June 2001. If the decision to continue development is made, additional funding will be needed to continue the program.	Medium	(9.8)
Ketolide Japan	Japan Phase I/III studies have been milestones funded. If positive data is available in the 4Q (this is the projected start date of the study), funding will be needed to stay on target with the expectations of Japan regulators.	Medium	(4.0)
Quinolone Milestone Payment	Currently, Phase Ib milestone payment is unfunded. If current enrollment levels are achieved for Phase Ib, additional funding will be necessary to satisfy our contractual obligations. There is a high probability that the contract will be re-negotiated and the milestone payment will then come due in 1Q 2002.	Medium	(3.5)
Subtotal for Medium Probability Scenarios			(17.3)
Immunosuppressant Sale	Sale of this compound is expected in 2001. Global Pharmaceutical R&D Division could potentially receive the revenue from this sale.	Low	5.0
Karo Bio DDC	If Karo Bio does not produce a DDC, we will not owe them a milestone payment in 2001.	Low	1.0
Blinacromal Funding	Go/No go decision is expected in late 1Q or early 2Q 2001. If the decision to continue development is made, Phase III studies will require funding.	Low	(11.7)
Subtotal for Low Probability Scenarios			(5.7)

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2001 PLAN  
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT

<u>NEUROLOGY</u>	
In	Out
Depakote	<ul style="list-style-type: none"> <li>- New formulations: epilepsy &amp; migraine</li> <li>- Bipolar in pediatric mania</li> <li>- Dose Proportionality</li> <li>- Pediatric Patient Extension - Psych</li> <li>- Acute Migraine</li> <li>- Depakote Status Epilepticus</li> </ul>
ABT-554	<ul style="list-style-type: none"> <li>- Milestone funded to Go/No Go decision June 2001 for neuropathic pain</li> <li>- Phase IIB Chronic Persistent Pain</li> </ul>
COX - II	<ul style="list-style-type: none"> <li>- Completion of work started in 2000 bringing it to a logical stopping point</li> <li>- Continuation of pre clinical and Phase I studies</li> </ul>
ABT-089	<ul style="list-style-type: none"> <li>- Completion of work started in 2000 bringing it to a logical stopping point</li> <li>- Single/Multiple rising dose Ph I study</li> </ul>
ABS-103	<ul style="list-style-type: none"> <li>- Completion of work started in 2000 bringing it to a logical stopping point</li> <li>- Pre clinical studies</li> <li>- Single rising dose Ph I study</li> </ul>
NPS-1776	<ul style="list-style-type: none"> <li>- Completion of work started in 2000 bringing it to a logical stopping point</li> <li>- Pre clinical studies</li> <li>- Single and rising multiple dose Ph I study and formulation bio studies</li> </ul>
Hydrocodone/lidocaine	<ul style="list-style-type: none"> <li>- Rapid dissolve and controlled release forms</li> </ul>
<u>ANTI INFECTIVE</u>	
Clarithromycin	<ul style="list-style-type: none"> <li>- Extended Release Once/Day</li> <li>- Phase IV Ind</li> <li>- Cystic Fibrosis</li> <li>- Asthma</li> </ul>
Ketolide	<ul style="list-style-type: none"> <li>- Tablet: FDA delayed review forcing ABT to add new sites and redo tissue studies to maintain NDA filing date. Cost = \$5.5MM</li> <li>- Drug Interaction studies: Warfarin, Digoxin &amp; Geriatric #17</li> <li>- I.V.</li> <li>- Pediatric</li> <li>- Japan Ph III</li> <li>- Drug Interaction studies: Lorazepam, Carbamazepine &amp; Cyclosporine</li> </ul>
Quinolone	<ul style="list-style-type: none"> <li>- Tablet</li> <li>- \$3MM milestone payment for Initiating Ph IIA</li> <li>- Milestone payment for initiation of Ph IIB \$3.5MM</li> </ul>
Neuraminidase (ABT-677)	<ul style="list-style-type: none"> <li>- 2 week toxicology study</li> <li>- single rising dose study</li> <li>- multiple rising dose study</li> </ul>
Omnicef	<ul style="list-style-type: none"> <li>- Otitis Media</li> <li>- AECB &amp; Pharyngitis</li> </ul>

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UROLOGY/CARDIOLOGYFenofibrate (Fournier)

In	Out
- Medical Affairs / Ph IV base level support	- Diabetics - PM Women - Feno Post MI

KCO

- Pre Clinicals

HIVRitonavir

- Norvir / Roche Combo  
- Ertac A & B

Kaletra

- IBHSC/Aaradex  
- Knoll (SEC reformulation)  
- HAART Metabolic complications  
- Start Phase IIIB Switch & Sustiva  
- Expanded Access  
- Ph II Pediatric  
- Ph III Naïve

- Current assumption is that long term safety data from completed portion of Ph II Pediatric and Ph III Naïve studies will suffice for FDA requirements. If the FDA requires us to finish those studies we will need about \$1.2MM.

Cyclosporine

- PREFER  
- European Switch Kidney plus Extension  
- Pediatric PK

CANCEREndothelin (ABT-627)

- Ph III pivotal study #1  
- Initiate Ph III pivotal study #2  
- QTC  
- Bioequivalence  
- Drug Interaction studies: Fexofenadine

- Early Stage Pca  
- Ph II exploratories  
- Drug Interaction studies: Midazolam, Ketoconazole & Rifampin

TSP #1 (ABT-510)

- Multiple dose in cancer patients  
- IND study

- Manufacturing & Toxicology

Metalloproteinase

- Multiple dose in cancer patients  
- IND study

- Manufacturing & Toxicology

Anti-Mitotic (ABT-751)

- Multiple dose in cancer patients  
- IND study

K-5

- Pre clinical / Ph I studies

FTI #2

- Pre clinical / Ph I studies

Other New Products

- DDC's & In - licensing

Other

- ADF, Exploratory, AEGIS Medra, productivity projects  
- Bimodolmol

Discovery

- Genaset

Analgesia Venture  
ABT-594  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
Neuronal nicotinic receptor antagonist (Milestone Funded to Go/No Go June, 2001)	9,300	14,411	9,307	(7)

Key Milestones / Assumptions	00 AGU	01 PLAN	Status (on target, pending or delayed to x)
• IND Filing	2/98	2/98	Completed
• Initiate Phase II - U.S.	7/98	7/98	Completed
• Go/No Go Clinical Efficacy (Phase IIa)	9/99	9/99	Completed
• Go/No Go Clinical Efficacy (Phase IIb)	2/01	6/01	Completed
• Initiate Phase III - U.S.	9/01	4/02	Delayed
• File NDA U.S./ EMEA EU	5/03	9/03	Delayed
			Last patient enrolled 1/5/01, n = 269

PARD	00 AGU	01 PLAN	
• Analytics Dev & Support	879	641	Analysis P, Support Mitsunobu Chem & Process Justification
• Formulation Dev & Support	745	226	Formulation scale-up and process optimization
• Clinical Finishing	607	145	Completion of M99-114, Pkging 3 Ph I study supplies
• Project Management Support	178	63	Coordination of activities and support of go/no go meeting prep
• PARD Total	2,409	1,075	

Total Venture Management				
• Expense: \$3,988, reflecting milestone funding				
• Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, then 11 headcount after July, 2001				

Clinical Grants	Int Patient Dosed	Last CRF	R/oss 2000 AGU	Start	End	2001 PLAN Start	End	Total	00 AGU	01 PLAN	Variance
<u>Phase I</u>											
M98-971	Human Metabolism 3H	Apr-01	Nov-01	Apr-01	Dec-01	Apr-01	Dec-01	165			165
TBD	fMRI	Aug-01	Nov-01	Feb-01	Nov-01	Feb-01	Nov-01	300			300
TBD	Titration Optimization	Apr-01	Jul-01	Mar-01	Sep-01	Mar-01	Sep-01	500			500
<u>Phase IIb</u>											
M99-114	Neuropathic Pain	Apr-00	Mar-02	Apr-00	Nov-00	Apr-00	May-01	3,100	3,000		100 A
Total								4,065	3,000		1,065

A Increased cost result of additional CRO monitoring costs.

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Analgesia Venture  
ABT-089  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
Neuronal nicotinic receptor modulator (Unfunded)	600	3,000	613	(13)

Key Milestones / Assumptions	00 AGU	01 PLAN TBD	Status (on target, pending or delayed to x) Unfunded, program on hold
- Transition Team Go/No Go			
-			
-			
-			
-			

PARD	00 AGU	01 PLAN
- Analytics Dev & Support	156	...
- Formulation Dev & Support	147	...
- Clinical Finishing	34	...
- Project Management Support	29	...
- PARC Total	366	...

Total Venture Management	SPD Requirements			
- Expense: \$3,988, reflecting milestone funding	Kgs	Heads	Mat'l Cost	Total Cost
- Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, then 11 headcount after July, 2001	2000 AGU	...	...	...
	2001 PLAN	...	...	...

Clinical Grants	1st Patient	Last	Dosed	CRF	R/oss	2000 AGU	2001 PLAN	Cost
Phase I						Start	End	Total
						Start	End	00 AGU
						Start	End	01 PLAN
						Start	End	Variance

Total

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# PART 2

Analgesia Venture  
ABS-103  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
ABS - 103 (Unfunded)	...	...	...	...

Key Milestones / Assumptions	00 AGU	01 PLAN 4/2001	Status (on target, pending or delayed to x)
• DDC Meeting			
•			
•			
•			
•			

PARD	00 AGU	01 PLAN
• Analytics Dev & Support	...	...
• Formulation Dev & Support	...	...
• Clinical Finishing	...	...
• Project Management Support	...	...
• PARD Total	...	...

Total Venture Management	00 AGU	01 PLAN
• Expense: \$3,988, reflecting milestone funding	...	...
• Authorized Heads: Flat to AGU until July, 2001, APT-594, Go/No Go Decision, then 11 headcount after July, 2001	...	...

Clinical Grants	1st Patient Dosed	Last CRF	R/oss 2000 AGU	R/oss 2001 PLAN	Cost 00 AGU	Cost 01 PLAN	Variance
			Start	End	Total		

Phase I

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Total	...	...	...	...	...	...	...
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**Analgesia Venture  
NPS 1776  
2001 PLAN KEY STATISTICS Pass II  
(\$000)**

<u>Project</u>	<u>2001 Target</u>	<u>2000 AGU</u>	<u>2001 PLAN</u>	<u>Target vs PLAN Fav(Unfav) Var</u>
NPS-1776 (Unfunded)	500	...	537	(37)

<u>Key Milestones / Assumptions</u>	<u>00 AGU</u>	<u>01 PLAN</u>	<u>Status (on target, pending or delayed to x)</u>
• DDC Meeting		4/2001	
•			
•			
•			
•			

<u>PARD</u>	<u>00 AGU</u>	<u>01 PLAN</u>
• Analytics Dev & Support		..
• Formulation Dev & Support		..
• Clinical Finishing		..
• Project Management Support		..
• PARD Total	..	..

<u>Total Venture Management</u>	<u>Kgs</u>	<u>Heads</u>	<u>Mat'l Cost</u>	<u>Total Cost</u>
• Expense: \$3,988, reflecting milestone funding	..	..	..	..
• Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, then 11 headcount after July, 2001	..	..	..	490

<u>Clinical Grants</u>	<u>1st Patient Dosed</u>	<u>Last CRF</u>	<u>R/oss</u>	<u>2000 AGU</u>	<u>2001 PLAN</u>	<u>Cost</u>
				<u>Start</u>	<u>End</u>	<u>Total</u>
						<u>00 AGU</u>
						<u>01 PLAN</u>
						<u>Variance</u>

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**Total**

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**ANTHINFECTIVE FRANCHISE  
CLARITHROMYCIN  
2001 PLAN KEY STATISTICS  
(\$000)**

Indication	2000 AGU	2001 Plan	2001 PLAN Fav/(Unfav) vs. AGU
Extended Release Once/Day	10,688	5,465	5,223
Pediatric New Strength (MHC)	107	41	66
XL/MR Patent Protection world wide (PARD/IDC)	883	152	731
AI Pediatric	4,573	30	4,543
Phase IV Init.	3,091	9,395	(6,304)
AI 1 Gram Tablet	2,985	11	2,974
Japan 400MG Tablet	1,881	0	1,881
Other	2,109	584	1,525
Total Clarithromycin	26,317	15,678	10,639
Plan Target	26,400	14,900	(11,500)
Variance Fav/(Unf) vs. target	83	(778)	(861)

Key Milestones / Assumptions	'00 AGU	'01 PLAN	Status
Extended Release Once/Day			
• Initiate BAL study Label addition for Biaxin XL	---	8/00	Complete
• Initiate Mucolytic - Private IND Studies (Investig. Initiated)	---	9/00	Complete
• Initiate Immunomodulatory Program - Private IND Studies (Investig. Initiated)	---	9/00	Complete
• Initiate Pertussis study (Investigator Initiated)	---	TBD	
PARD	AGU	'01 PLAN	Status
• Patent protection effort for XL and MR formulations	1/00	1/01	Ongoing
	AGU	2001 PLAN	2001 vs AGU Fav/(Unf)
• Budget (\$000)			PARD Variance by Project:
Analytical Development & Support	879	335	544
Formulation Development & Support	2,061	231	1,830
Clinical Finishing	299	358	(59)
Project Mgt.	320	137	183
Total	3,559	1,061	2,498
			ER Once/Day 1,284
			Ped New Stre 107
			AI Ped 1/Day 449
			Patent 631
			Other 47
			2,498

**Venture Management (Total Department)**

- Expense:
- \$12,020M (Increase of \$3,584M vs 2000 Actual; Includes ABT-492 Milestone payment of \$3MM, \$3MM Milestone Payment)
- Total Heads - 41, unchanged vs. AGU. Abbott full time - 38, unchanged vs. AGU.

**CAPD Requirements**

	Kgs	Heads	Mat'l Cost	Total Cost
AGU	0	0	328	328 A
2001	0	0	0	0

A) Project budget does not include Phase IV bulk drug development expense (process improvement) of \$4.7MM; \$326M included in AGU for 14-OH metabolite.

Domestic Studies	1st Patient Dosed	Last CRF	R/OSS 2000 AGU Start End	R/OSS 2001 PLAN Start End	Study Total	Cost(\$000) '00 ACT '01 PLAN	2001 Fav/(Unf.) vs. AGU
Accrual Adjustments - Completed Studies						(2,529) 0	(2,529)
Extended Release Once/Day							
M99-066 Biaxin XL vs. Augmentin in AECB (300 pts)	9/99	4/00	9/99	4/00	3,900	1,277 0	1,277
M99-077 Biaxin XL vs. Levofloxacin in CAP (replace Trova 300 pts)	9/99	7/00	9/99	7/00	4,000	2,333 0	2,333
M99-083 Biaxin XL + Ceph. IV Step Down study vs Lev. (150 pts)	1/00	12/00	1/00	12/00	500	357 500	(143)
M99-066B Biaxin XL Immunomodulatory Claim	1/00	12/00	1/00	12/00	500	527 0	527
M00-206 Biaxin XL Mucolytic - Private IND Studies (Inv. Init.; 30 pts.)	9/00	12/01	9/00	12/01	180	0 180	(180)
M00-208 Biaxin XL Mucolytic - Private IND Studies (Inv. Init.; 50 pts.)	9/00	12/01	9/00	12/01	180	0 180	(180)
M00-207 Biaxin XL Immunomodulatory - Private IND (Inv. Init. pat. TB	3/00	12/02	3/00	12/01	880	0 880	(880)
* Note: M00-206, M00-207, M00-208 continuations of M99-066B							
M00-214 BAL study Label addition for Biaxin XL (45 patients)	8/00	4/01		8/00	350	350 0	350
TBD Pertussis Investigator Initiated study (patients TBD)	TBD	TBD		TBD	150	0 150	(150)
N/A Counter Resistance - Animal In Vitro studies CAP registry	N/A	N/A		N/A	500	0 1,050	(1,050)
<b>Total Domestic:</b>					<b>11,140</b>	<b>2,315</b>	<b>2,940</b>
International							
W99-317 PRSP/DRSP IR	11/99	8/00	11/99	8/00	3,249	2,500 749	1,751
Pediatric (International)							
Multiple AI Ped Once-A-Day	1/00	12/02	1/00	12/02	6,707	1,300 0	1,300
Other (International)							
Multiple AI 1 Gram PK Studies	1/00	12/02	1/00	12/02	2,790	850 0	850
Multiple AI Japan 400MG Tablet	1/00	12/02	1/00	12/02	3,488	1,033 0	1,033
Multiple Clari MR	1/01	12/01		1/01	0	0 0	0
Multiple Clari OD XL vs. MR	4/00	12/02	4/00	12/02	9,056	550 5706	(5,156)
MECAPP						0 848	(848)
Italy Wheezes (Included in Domestic - Immunomodulatory)						0 0	0
<b>Total International (Excluding IDC of \$4,695M in '00; \$315 in '01):</b>					<b>25,290</b>	<b>6,233</b>	<b>7,303</b>
<b>Total:</b>					<b>36,430</b>	<b>8,548</b>	<b>10,243</b>

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**ANTI-INFECTIVE FRANCHISE**  
**Ketolide ABT-773**  
**2001 PLAN KEY STATISTICS**  
**(\$000)**

Project	2000 Actual	2001 PLAN	2001 PLAN vs. '00 Actual Fav/(Unfav)
<b>KETOLIDE ABT-773</b>			
Tablet	67,887	68,574	(2,687)
Pediatric	2,862	8	2,874
Japan Formulation/Registration	2,957	1,628 C	1,329
IV	1,000 A	64	936
	74,525	90,274	(15,748)
Target	74,100	88,000	13,900
Variance Fav/(Unf.) vs. Target	(428) A	(2,274) B	(1,846)
A) Unfunded IV Project responsible for variance from target. B) Variance expected to be reduced in APU by reduction of one SPD bulk drug campaign (\$1.6MM) and reduction in International support to Japan registration (\$3.4MM). C) Japan Registration estimate for 2001 assumes delay in Phase I/II studies to 2002.			
<b>Key Milestones / Assumptions</b>	'00 AGU	'01 PLAN	
Complete Phase IIB	6/00	6/00	Complete
End of Phase II - FDA Meeting	10/00	12/00	Complete; Protocol changes will delay Europe start.
Initiate Phase III - North America / Europe	11/00	11/00	Phase III delayed; Studies will start 4Q 00, Europe 1Q 01
Initiate Phase III - South Africa / South America		4/01	Additional sites to achieve required patients by NDA filing date
Pediatric Formulation Go / No-Go	8/00	11/00	No funding for Pediatric in 2001.
SPD Bulk Drug: (Year 2001: 5 deliveries of 335KG = 1,675KG Total)	1/01-12/01	1/01-12/01	Discussing with SPD the possibility for reduction of one delivery
Initiate Phase III CAP / Sinusitis comparator studies	9/01	11/01	On target (Based on CAP / Sinusitis 150mg QD vs. 150mg BID results).
Fda Tablet NDA	8/02	8/02	NDA Filing delayed to 3Q 2002
Fda Pediatric and IV NDAs	TBD	TBD	No funding for Pediatric or IV in 2001 Plan.
<b>PARD</b>	'00 AGU	'01 PLAN	Status (on target, pending or delayed to x)
Scale Up activities 75L	9/99-1/00	9/99-1/00	Complete
Intermediate scale up 300L	12/99-2/00	12/99-2/00	Complete
<b>Budget</b>			2001 Plan vs. AGU Fav/(Unf.)
Analytical Development & Support	2,061	1,723	338
Formulation Development & Support	2,223	1,458	765
Clinical Finishing	1,845	1,478	367
Project Mgt.	547	567	(20)
<b>Total</b>	<b>6,676</b>	<b>5,224</b>	<b>1,452</b>

**Venture Management**

Expense:  
\$12,020M (Increase of \$3,564M vs 2000 Actual; includes ABT-492 Milestone payment of \$3MM.  
Total Heads - 41, unchanged vs. AGU. Abbott full time - 39, unchanged vs. AGU.

**SPD Requirements**

	Kgs	Heads	Direct Cost	Task	Total Cost
2000 AGU	2,520	A	16,809	B	22,632
2001 PLAN	1,675 C)	22	9,408		14,970 C)
A) 2198 Kgs for Tablet Formulation, 242 Kgs for Pediatric, 80 Kgs for IV at \$7,500 / Kg. Total CAPD costs include headcount related charges of \$7,343M. B) 2,520 Kgs @ \$7,500/kg for \$18.9MM less net prepaying \$2.1MM. (\$6,667/kg net of task) C) 1,675 Kgs @ \$5,000/kg + headcount and prepaying charges of \$6,595M. Does not reflect planned reduction of one bulk drug campaign.					

	1st Patient Dosed	Last CRF	R/OSS 2000 AGU Start	R/OSS 2000 AGU End	R/OSS 2001 PLAN Start	R/OSS 2001 PLAN End	Study Total	Cost(\$000) 2000 Act.	Cost(\$000) 2001 PLAN	2001 Fav/(Unfav.) vs. AGU
<b>ACPRU STUDIES (Initiated in 2001)</b>										
Bio 300L-1200L	5-01				5-01	12-01	216	216		(216)
Bio 300L-800L BE	11-01				11-01	6-02	231	231		(231)
Drug Interaction Lorazepam - (delayed to 2002)	TBD				TBD	TBD	175			
Drug Interaction Warfarin	2-01				2-01	8-01	214	214		(214)
Drug Interaction Digoxin	1-01				1-01	7-01	372	372		(372)
Drug Interaction Carbamazepine (delayed to 2002)	TBD				TBD	TBD	215			
Drug Interaction Cyclosporin (delayed to 2002)	TBD				TBD	TBD	280			
Drug Interaction Gentamicin #17	10-01				10-01	10-02	162	162		(162)
ABT-773 Site 65L to 300L	5-01				5-01	10-01	175	175		(175)
<b>ACPRU Total New 2001 Studies</b>									1,370	(1,370)
<b>PHASE IIB STUDIES</b>										
M99-054 CAP	9-99	6/00	9-99	6/00	9-99	6/00	4,089	1,637		1,637
M99-053 Sinusitis	9-99	6/00	9-99	6/00	9-99	6/00	3,172	1,558		1,558
M99-048 AECB	9-99	6/00	9-99	6/00	9-99	6/00	3,885	2,212		2,212
Writing							210	157		157
<b>TOTAL PHASE IIB STUDIES</b>							11,356	5,564		5,564
<b>2000 External Bio Studies</b>										
M99-119 Japan Phase I	12/99	4/00	12/99	4/00	12/99	4/00	957	790		790
M99-142 Tissue Studies	3/00	12/00	3/00	12/00	3/00	12/00	469	489		469
Tissue Study - Cefixime - 150mg	3/01	12/01			3/01	12/01	500		500	(500)
Tissue Study - Gatifloxacin - 150mg QD vs. 150mg BID	3/01	12/01			3/01	12/01	500		500	(500)
M99-128 Renal	9/00	2/01	9/00	2/01	9/00	2/01	300	89	138	(89)
Hepatic	3/00	3/01	3/00	3/01	3/00	3/01	313	251	62	189
							2,539	1,579	1,200	379
<b>JAPAN STUDIES (New Formulation)</b>										
Japan Phase I	10/00	5/01	10/00	5/01	10/00	5/01	1,800	1,800		1,800
Japan Phase I/II					9/01	4/03	22,000			
							23,800	1,800		1,600
<b>PHASE III STUDIES</b>										
Multiple	6/00	6/00	6/00	6/00	6/00	6/00	1,306	1,306		1,306
M00-221 (M99-089) CAP - Levo 500mg QD, NA/SA (450 pat.)	9/01	3/02	9/01	3/02	11/01	5/02	8,200		2,343	(2,343)
M00-219 (M00-152) CAP - Open Label NA (800 pat.)	11/00	6/01	11/00	6/01	11/00	9/01	16,286	3,535	12,731	(9,196)
M00-220 (M00-151) CAP - Amoxicillin + Azid. EU (500 pat.)	9/01	3/02	9/01	3/02	11/01	5/02	5,700		1,629	(1,629)
M00-226 (M00-149) Sinusitis - Cefuroxime 250mg BID, NA (450 pts.)	9/01	3/02	9/01	3/02	11/01	5/02	4,400		1,257	(1,257)
M00-225 (M00-087) Sinusitis - Open Label, NA/SA, EU (800 pts.)	11/00	6/01	11/00	6/01	11/00	9/01	9,256	2,037	7,219	(5,182)
M00-218 (M00-150) Sinusitis - vs. Augmentin 875mg BID, EU (500 Pats)	9/01	3/02	9/01	3/02	11/01	5/02	5,300		1,514	(1,514)
M00-260 Sinusitis Double Tap	4/01	6/02			4/01	6/03	850		510	(510)
M00-216 (M99-088) ABECS - Levo 500mg QD, NA	11/00	6/01	11/00	6/01	11/00	6/01	7,721	1,930	5,791	(3,881)
M00-217 (M99-143) ABECS - Azithromycin NA, EU, SAF	11/00	6/01	11/00	6/01	11/00	9/01	5,224	1,188	4,036	(2,848)
M00-223 (M00-090) Pharyngitis - Penicillin 250 TID, NA/SA (520 pat)	11/00	6/01	11/00	6/01	11/00	6/01	4,739	1,185	3,554	(2,369)
M00-222 (M00-157) Pharyngitis - Penicillin 500mg QID, EU (520 pat.)	11/00	6/01	11/00	6/01	11/00	9/01	4,629	1,054	3,575	(2,521)
							73,591	12,235	44,159	(31,524)
<b>Other Studies</b>										
A.D. Little Pediatric Taste Testing	3/00	2/01	3/00	2/01	3/00	2/01	270	225	45	180
Completed Pediatric Prototype Studies	6/00	12/00	6/00	12/00	6/00	12/00	225	(250)		(250)
Microbiology PK/PD Studies	1/00	12/01	1/00	12/01	1/00	12/01	3,500	1,811	2,000	(189)
Pediatric PK/PD, Phase II	6/00	8/00	6/00	8/00	6/00	8/00	1,500	331		331
<b>GRAND TOTAL (EXCLUDING ACPRU)</b>							116,581	23,095	47,404	(24,389)

**ANTI-INFECTIVE FRANCHISE  
QUINOLONE ABT-492  
2001 PLAN KEY STATISTICS  
(\$000)**

Indication	2000 Actual	2001 PLAN	2001 PLAN Fav/(Unfav) vs. Actual
Development	7,063	21,341	(14,278)
Milestone Payment (Phase IIA)	0	3,000	(3,000)
Total Quinolone	7,063	24,341	(17,278)
Target	6,800	25,000	(18,200)
Variance Fav/(Unf) vs. target	(263)	859	922

Key Milestones / Assumptions	'00 AGU	'01 PLAN	Status
• INITIATE PHASE I STUDIES	4Q '00	4Q '00	Complete
• INITIATE PHASE IIA SAFETY STUDY	---	3Q '01	On target
• NDA Filing	4Q '03	4Q '04	Delayed one year due to funding limitation.

PARD	'00 AGU	'01 PLAN	
• Formulation Development			
IOC Phase II	---	1/01	On target
PARD Commercial	---	5/01	On target
• Budget (PARD)			
Analytical Development & Support	225	515	(290)
Formulation Development & Support	274	341	(67)
Clinical Finishing	36	10	26
Project Mgt.	59	85	(36)
Total	594	961	(367)

**Venture Management (Total Department)**

- Expense:  
\$12,620M (Increase of \$3,584M vs 2000 Actual; includes ABT-492 Milestone payment of \$3MM, \$3MM Milestone Payment)
- Total Heads - 41, unchanged vs. AGU. Abbott full time - 39, unchanged vs. AGU.

**CAPD Requirements**

	Kgs	Heads	Pilot Plant	Personnel	Total Cost
AGU	0	0.5	480	118	598 A
2001 PLAN	600	6.0	1892	1,470	5,762 B

A) CAPD Pilot Plant 12 weeks @ \$40M/week and 1 person for 6 months  
B) CAPD Pilot Plant 44 weeks @ \$43M/week, 6 headcount @ \$245M, 600kg of bulk drug.

	1st Patient Dosed	Last CRF	R/OSS 2000 AGU Start	R/OSS 2000 AGU End	R/OSS 2001 PLAN Start	R/OSS 2001 PLAN End	Study Total	Cost(\$000) 2000 Act.	Cost(\$000) 2001 PLAN	2001 Fav/(Unfav.) vs. 2000 Act.
<b>Phase I</b>										
Single Dose/ Food Effect in Healthy Volunteers (108 pat)	11/00	01/01	4Q 2000	4Q 2000	9/00	01/01	850	680	170	510
Multiple Rising Doses in Healthy Volunteers (60 patients)	01/01	03/01	4Q 2000	4Q 2000	02/01	06/01	500	0	500	(500)
Phase IA / Bio Studies (3 studies)			04/01	09/01	04/01	09/01	700		700	(700)
<b>PHASE I TOTALS</b>							2,050	680	1,370	(680)
Microbiology Studies							710	0	710	(710)
<b>Phase IIA</b>										
AECB (250 patients)	06/01	04/02			08/01	04/02	3,750	0	2,083	(2,083)
<b>SUBTOTAL PHASE I / PHASE IIA</b>							6,510	680	4,163	(3,483)
<b>Phase IIB</b>										
CAP (250 patients)	11/01	07/02			11/01	07/02	3,750	0	837	(837)
Uncomplicated UTI (300 patients)	01/02	09/02			01/02	09/02	1,650	0	0	0
Skin and Skin Structure Infection (300 patients)	01/02	12/02			01/02	12/02	2,100	0	0	0
<b>PHASE II B TOTAL</b>							7,500	0	837	(837)
<b>Total</b>							14,010	680	5,000	(4,320)

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**ANTI-INFECTION FRANCHISE  
OMNICEF  
2001 PLAN KEY STATISTICS  
(\$000)**

Indication	2000 AGU	2001 PLAN	2001 PLAN Fav/(Unfav) vs. AGU
Development	0	4,843	(4,843)
	0		0
Total	0	4,843	(4,843)
Target	0	5,000	(5,000)
Variance Fav/(Unf) vs. target	0	157	157

Key Milestones / Assumptions	'00 AGU	'01 PLAN	Status
• INITIATE ACUTE OTITIS MEDIA STUDY		09/01	On Target

PARD	'00 AGU	'00 AGU	Status
• To be defined			
•			
• Budget	'00 APU	'00 AGU	AGU vs APU Fav/(Unf)
Clinical Finishing	0	92	(92)
Project Mgt.	0	0	0
Total	0	92	(92)

**Venture Management (Total Department)**

- Expenses:  
\$12,020M (Increase of \$3,564M vs 2000 Actual; includes ABBT-492 Milestone payment of \$3MM, \$3MM Milestone Payment)
- Total Heads - 41, unchanged vs. AGU. Abbott full time - 33, unchanged vs. AGU.

CAPD Requirements	Pilot	Personnel	Total Cost
Kgs	Heads	Plant	
AGU	0	0	0
2001 PLAN	0	0.0	0

Phase	1st Patient Dosed	Last CRF	R/OSS 2000 AGU		R/OSS 2001 PLAN		Study Total	Cost(\$000)		2001 Fav/(Unfav.) vs. AGU
			Start	End	Start	End		2000 AGU	2001 PLAN	
Phase IV										
Acute Otitis Media 3 Arm 5D QD BID vs. Zithromax (250 pat)	06/01	07/02			08/01	05/02	6,000		3,000	(3,000)
PHASE IV TOTALS							6,000		3,000	(3,000)
<b>Total</b>							6,000	0	3,000	(3,000)

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UROLOGY  
KCO ABT-598  
2001 PLAN KEY STATISTICS  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	PLAN vs TARGET Fav(Unfav) Var
Project Name KCO ABT-598	4500	0	4960	(460)

**Key Milestones / Assumptions**

- First Study
- Second Study
- Feasibility of ER Prototypes completed
- Go/No go Decision

00 AGU	01 PLAN	Status (on target, pending or delayed to x)
N/A	11/01	On target to PLAN
N/A	5/02	On target to PLAN
N/A	11/02	On target to PLAN
N/A	11/02	On target to PLAN

**PARD**

- Analytics Dev & Support
- Formulation Dev & Support
- Clinical Finishing
- Project Management Support
- PARD Total

00 AGU	01 PLAN
...	326
...	221
...	56
...	43
...	646

Support Discovery

**Total Venture Management**

- Expense: Plan expense at \$1,328.
- Authorized Heads: D-42U headcount at 14. KCO estimated equivalents 5.9

**Discovery Requirements**

	Kgs	Heads	Matl Cost	Total Cost
2000 AGU	...	...	...	...
2001 PLAN	...	...	...	...

Clinical Grants Protocol Pre-Phase I TBD TBD Phase I	Study Name SD Escalating Dose Rate of Rise	1st Patient Dosed	Last CRF	R/oss		Cost			
				2000 AGU Start	2001 PLAN End	Total	00 AGU	01 PLAN	Variance
		11/01	2/02	11/01	2/02	760	0	380	(380)
		5/02	6/02	5/02	8/02				

Phase II

Phase III

Total

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**ANTI-VIRAL  
NORVIR ABT-538  
2001 PLAN KEY STATISTICS  
(\$000)**

<u>Project</u>	<u>2001 Target</u>	<u>2000 AGU</u>	<u>2001 PLAN</u>	<u>PLAN vs TARGET Fav(Unfav) Var</u>
Venture Programs				
Phase-IV Programs	2,000	8,530	1,780	220
Total	4,000	13,000	4,020	(240)
				(20)

**Key Milestones / Assumptions**

	<u>00 AGU 2001</u>	<u>01 PLAN 2001</u>	<u>Status (on target, pending or delayed to x)</u>
- Continue combination studies			Ongoing

**PARD**

- Analytics Dev & Support
- Formulation Dev & Support
- Clinical Finishing
- Project Management Support

PARD Total

**total Venture Management**

Expense: \$993M: \$283 for Venture \$710 for PHASE IV  
Authorized Heads: Total 6 heads: 1 Venture, 5 PHASE IV

<u>SPD Requirements</u>			
	<u>Kgs</u>	<u>Heads</u>	<u>Mat'l Cost</u>
2000 AGU	...	...	...
2001 PLAN	...	...	...

<u>Initial Grants</u>	<u>Protocol</u>	<u>Study Name</u>	<u>1st Patient Dosed</u>	<u>Last CRF</u>	<u>R/oss</u>	<u>2000 AGU</u>	<u>2001 PLAN</u>	<u>Cost</u>	<u>Variance</u>
						<u>Start</u>	<u>End</u>	<u>Total</u>	<u>00 AGU</u>
<b>ENTURE STUDIES</b>									
M98-985	RTV/IDV Combo Study		7/99	12/00		7/99	12/00	909	450
<b>PHASE IV STUDIES</b>									
M98-482	Norvir/Roche Combo								
M98-824	Erica A		4/96	TBD		4/95	07/02	3,050	-50
M99-019	Erica B		4/00	TBD		7/99	12/02	1,719	527
M99-047	NICE		4/00	TBD		7/99	12/02	1,889	582
<b>ITAL PHASE IV STUDIES</b>									
			9/99	TBD		7/99	12/01	2,172	1,448
								8,830	2,507
								1,067	1,440

**OTHER STUDIES**

M99-627 Promethesus - final payment

total

750	0	200	(200)
9,580	2,507	1,267	1,240

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**ANTI-VIRAL  
KALETRA ABT-373  
2001 PLAN KEY STATISTICS  
(\$000)**

Project	2001 Target	2000 AGU	2001 PLAN	PLAN vs TARGET Fav(Unfav) Var
Venture Programs	44,100	75,954	45,005	...
Phase-IV Programs (Metabolic and Switch)	6,800	546	6,800	...
Total Project	50,900	76,500	51,805	(905)

Key Milestones / Assumptions	00 AGU		01 PLAN		Status (on target, pending or delayed to t)
	8/01	12/02	6/02	12/02	
- Complete International EAP program				On Target	
- Continue Regulatory requirements				Approved in 2001 for \$3.8MM	
- Continue Kroll formulation				Ongoing	
- Start Phase IIIB Switch and Salvage Kaletra				Approved in 2001 for \$9.4MM	

PARD	00 AGU		01 PLAN		Continued FDA requirements and Clinical support
	3,175	462	6/02	12/02	
- Analytics Dev & Support	2,813	468			
- Formulation Dev & Support	3,000	700			
- Positive controls	3,251	1,089			
- Clinical Finishing	615	189			
- Project Management Support	12,954	2,808			
- PARD Total					

Total Venture Management	
- Expense: \$13,740 which includes \$1.5MM Bulk Drug and \$1.5MM contract agreements	
- Authorized Funds: 55 same as AGU	

Clinical Grants Protocol	Study Name	Roses		Roses		Cost	
		1st Patient Dosed	Last CRF	2000 AGU Start	End	2001 PLAN Start	End
<b>Phase II</b>							
M87-720	Phase II Naive	11/87	3/02	10/87	12/02	10/87	12/02
M87-785	Phase II Experience	6/88	3/02	4/88	12/02	4/88	12/02
M88-957	Phase II Salvage	6/88	8/01	6/88	8/01	6/88	8/01
M89-049	Experience Inc Dose	TBD	3/02	4/00	12/02	4/00	12/02
M88-840	PEDS Phase I/II	7/89	12/01	8/89	12/03	8/89	12/03
TBD	ACTG Misc Studies	N/A	N/A	8/00	12/04	8/00	12/04
M00-154	Acute Serocconversion	TBD	1/03	8/00	12/02	8/00	12/02
<b>Phase III</b>							
M88-883	Phase III Naive	3/89	12/01	11/88	12/01	11/88	12/01
M88-888	Phase III Experience	6/89	3/02	5/89	12/01	5/89	12/01
M89-056	Phase IIIb QD	3/00	12/01	11/89	12/02	11/89	12/01
M89-046	Expanded Access	8/89	3/03	9/89	8/01	9/89	12/02
<b>NEW VENTURE STUDIES</b>							
M00-256	Salvage of Kaletra	5/01	4/03	5/01	4/03	5/01	4/03
M00-287	Salvage of K2	5/01	4/03	5/01	4/03	5/01	4/03
TBD	Desipramine Interaction	8/01	10/01	8/01	10/01	8/01	10/01
TBD	Hepatic Impairment	7/01	8/02	7/01	8/02	7/01	8/02
TBD	Rilampri Interaction	10/01	4/02	10/01	4/02	10/01	4/02
TBD	Ampranavir Interaction	10/01	4/02	10/01	4/02	10/01	4/02
TBD	Pi Interaction	5/01	8/01	5/01	8/01	5/01	8/01
TBD	Bio Study Japan	3/01	8/02	3/01	8/02	3/01	8/02
TBD	Abbott France/Dur-Pon(BIKS)						
<b>Kroll Studies</b>							
TBD	Bio Study	4/01	7/01	4/01	7/01	4/01	7/01
TBD	Pharmacol	4/01	7/01	4/01	7/01	4/01	7/01
<b>Phase IV Program</b>							
M00-267	Switch Study	TBD	TBD	2/01	1/02	2/01	1/02
TBD	Metabolism - Concomitum / EMEA	...	...	01/01	12/03	01/01	12/03
TBD	Metabolism - Outside Studies	TBD	TBD	TBD	TBD	TBD	TBD
Total							

1st Patient Dosed	Last CRF	2000 AGU Start	End	2001 PLAN Start	End	Total	00 AGU	01 PLAN	Variance
11/87	3/02	10/87	12/02	10/87	12/02	7,308	0	0	...
6/88	3/02	4/88	12/02	4/88	12/02	3,631	764	500	264
6/88	8/01	6/88	8/01	6/88	8/01	1,787	588	581	7
TBD	3/02	4/00	12/02	4/00	12/02	1,062	488	325	183
7/89	12/01	8/89	12/03	8/89	12/03	5,022	2,005	980	1,015
N/A	N/A	8/00	12/04	8/00	12/04	3,025	175	100	75
TBD	1/03	8/00	12/02	8/00	12/02	614	106	254	(148)
3/89	12/01	11/88	12/01	11/88	12/01	26,176	8,000	4,178	3,824
6/89	3/02	5/89	12/01	5/89	12/01	11,118	4,041	1,188	2,873
3/00	12/01	11/89	12/02	11/89	12/01	1,495	682	528	158
8/89	3/03	9/89	8/01	9/89	12/02	22,525	10,720	4,725	5,995
5/01	4/03	5/01	4/03	5/01	4/03	1,820	-	880	(880)
5/01	4/03	5/01	4/03	5/01	4/03	1,180	-	540	(540)
8/01	10/01	8/01	10/01	8/01	10/01	188	-	188	(188)
7/01	8/02	7/01	8/02	7/01	8/02	900	-	500	(500)
10/01	4/02	10/01	4/02	10/01	4/02	1,184	-	500	(500)
10/01	4/02	10/01	4/02	10/01	4/02	750	-	320	(320)
5/01	8/01	5/01	8/01	5/01	8/01	320	-	203	(203)
3/01	8/02	3/01	8/02	3/01	8/02	285	-	320	(320)
4/01	7/01	4/01	7/01	4/01	7/01	220	-	150	(150)
4/01	7/01	4/01	7/01	4/01	7/01	221	-	220	(220)
TBD	TBD	...	...	2/01	1/02	5,424	-	4,815	(4,815)
...	...	11/00	12/00	01/01	12/03	324	-	286	38
TBD	TBD	...	...	TBD	TBD	TBD	-	388	(388)
Total						97,967	27,893	22,946	4,947

16-Jan-01

ONCOLOGY GROUP  
ATRASANTAN (ABT-627)  
2001 PLAN KEY STATISTICS  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	PLAN vs Target Fav(Unfav) Var
Endothelin Antagonist	39,200	13,000	38,643	557

Key Milestones / Assumptions	00 AGU 4Q/00	01 PLAN 5/01	Status (on target, pending or delayed to x)
- Phase III Pivotal Study (M00-211)		5/01	Delayed to 5/01.
- Initiate Phase III Pivotal Study #2 (M00-244)	--	6/01	Delayed to 6/01.
- Qtc, Bioequivalence and Drug Interactions	--	2Q/01	On target

PARD	00 AGU	01 PLAN	Notes
- Analytics Dev & Support	601	1,555	NDA lots and stability support, plus clinical study
- Formulation Dev & Support	440	833	supply and re-supply.
- Clinical Finishing	57	1,019	
- Project Management Support	59	195	
- PARP Total	1,156	3,602	

Total Venture Management	SPD Requirements
- Expense: \$7,246M of \$11,712M	Kgs 30 2 115 350
- Authorized Heads: 38 Regular and 9 Other	2000 AGU 2 2 683
	2001 PLAN
	No bulk deliveries are planned; process justification work continues

Clinical Grants	1st Patient Dosed	Last CRF	R/loss 2000 AGU	2001 PLAN	Cost	Variance
Phase II						
M96-594	2/98	TBD	8/97	12/99	9,858	...
M97-739	4/98	TBD	1/98	12/00	3,200	...
Clin Pharm	4/01	6/01	n/a	12/01	281	(281)
Clin Pharm	6/01	8/01	n/a	12/01	321	(321)
Clin Pharm	1Q/02	2Q/01	n/a	3Q/02	0	...
Clin Pharm	1Q/02	2Q/01	n/a	3Q/02	0	...
Clin Pharm	4/01	6/01	n/a	8/01	162	(162)
Clin Pharm	1Q/02	2Q/01	n/a	3Q/02	0	...
Phase III						
M00-211	5/01	8/03	12/00	8/03	1,950	12,420 (10,470)
M00-244	6/01	12/04	...	12/04	...	5,698 (5,698)
M00-258	TBD	TBD	...	12/04	11,000	846 (846)
TBD	TBD	TBD	...	12/04	2,000	288 (288)
Less Clin Pharm studies					(764)	(764)
Total					19,252	(17,302)

26-Jan

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**ONCOLOGY GROUP  
TSP (ABT-510)  
2001 PLAN KEY STATISTICS  
(\$000)**

Project	2001	2000	2001	PLAN vs Target
	Target	AGU	PLAN	Fav(Unfav) Var
Antiangiogenesis Thrombospondin	9,000	6,600	9,981	(981)

Milestones / Assumptions	00 AGU	01 PLAN	Status (on target, pending or delayed to x)	
	9/00	2/01 2Q/01 6/01	Delayed - Accommodate European Ethics Committee	On Target
Initiate Phase I Multiple Dose Study	-			
Pre-IND Meeting	-			
Initiate IND Study	-			

RD	00 AGU	01 PLAN	Notes
Analytics Dev & Support	391	525	
Formulation Dev & Support	211	355	
Clinical Finishing	74	165	
Project Management Support	86	105	
PARD Total	762	1,150	

Local Grants	SPD Requirements				Cost			
	Kgs	Heads	Mat'l Cost	Total Cost	2001 PLAN	00 AGU	01 PLAN	Variance
Multiple Dose In Cancer Patients	...	...	...	...	10/00	1,236	972	(272)
University of Texas - Dr. Fidler	7	5	480	2,538	5/00	300	81	144
University of Texas - Dr. Fidler	...	...	...	...	4/01	300	218	(218)
IND Study	...	...	...	...	6/01	400	350	(350)

Local Grants	1st Patient Dosed	Last CRF	2000 AGU	2001 PLAN	R/loss
			Start	End	
Multiple Dose In Cancer Patients	2/01	11/01	9/00	5/01	...
University of Texas - Dr. Fidler	...	...	5/00	3/01	...
University of Texas - Dr. Fidler	...	...	...	...	...
IND Study	6/01	1/02	...	...	...

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ABBT 0037557

Total	2,236	925	1,621	(696)
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**ONCOLOGY GROUP**  
**MMPI #2 (ABT-518)**  
**2001 PLAN KEY STATISTICS**  
**(\$000)**

<u>Project</u>	<u>2001 Target</u>	<u>2000 AGU</u>	<u>2001 PLAN</u>	<u>PLAN vs Target Fav(Unfav) Var</u>
Matrix Metalloproteinase Inhibitor	7,000	5,000	7,362	(362)

<u>Key Milestones / Assumptions</u>	<u>00 AGU</u>	<u>01 PLAN</u>	<u>Status (on target, pending or delayed to x)</u>
Initiate Phase I Multiple Dose Study	10/00	1/01	Delayed - due to safety related protocol revisions
Pre-IND Meeting	--	2Q/01	On Target
Initiate IND Study	--	8/01	On Target

<u>PARD</u>	<u>00 AGU</u>	<u>01 PLAN</u>	<u>Note:</u>
Analytics Dev & Support	276	546	Clinical Supplies for Phase I trial
Formulation Dev & Support	235	355	
Clinical Finishing	76	56	
Project Management Support	61	74	
PARD Total	648	1,031	

<u>Total Venture Management</u>	<u>SPD Requirements</u>	<u>Kgs</u>	<u>Heads</u>	<u>Mar'l Cost</u>	<u>Total Cost</u>
Expense: \$804M of \$11,712M	2000 AGU	..	..	..	..
Authorized Heads: 38 Regular and 9 Other	2001 PLAN	..	..	..	..

Clinical Grants			R/loss		2001 PLAN		Cost			
1st Patient Dosed	Last CRF		Start	End	Start	End	Total	00 AGU	01 PLAN	Variance
Phase I										
M00-235	Multiple Dose in Cancer Patients	2/01	1/02	10/00	12/00	11/00	1/02	960	375	768 (393)
TBD	IND Study	8/01	1/02	..	..	6/01	1/02	400	...	350 (350)

<u>Total</u>	<u>1,360</u>	<u>375</u>	<u>1,118</u>	<u>(743)</u>
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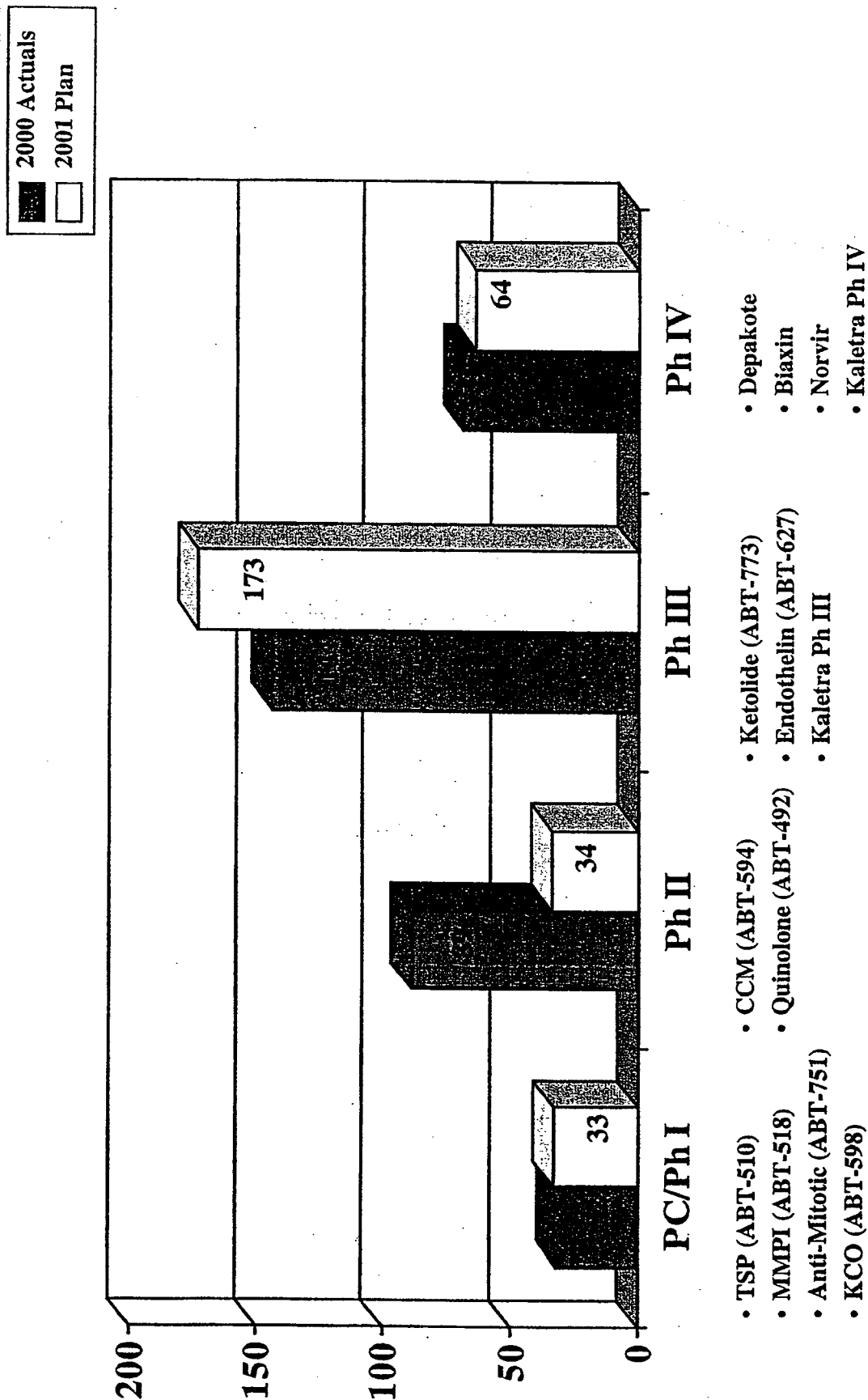
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**ABBT 00375558**

**Total**  
**30-Jan**

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# R&D Spending by Phase



**Global Pharmaceutical Research & Development  
Funding by Phase  
2001 PLAN**

	2000 Actuals	2001 PLAN
<b>Preclinical/Phase I</b>		
COX-II	2.7	1.2
ABT-089 (formerly ChCM)	1.6	0.6
ABS-103	...	...
NPS-1776	...	...
Quinolone	7.1	...
Neuraminidase	2.8	...
KCO	...	5.0
TSP #1	7.0	10.0
MMPI	5.6	7.4
Anti-Mitotic	3.9	8.4
K-5	1.0	...
<b>Subtotal PC/Phase I</b>	<b>31.7</b>	<b>32.6</b>
<b>Phase II</b>		
ABT-594	14.3	9.3
Ketolide	55.9	...
Quinolone	...	24.5
NS-49	1.9	...
Endothelin	16.8	...
<b>Subtotal Phase II</b>	<b>88.9</b>	<b>33.8</b>
<b>Phase III</b>		
Ketolide	18.6	88.0
BPH Backup	31.5	2.3
Kaletra	80.8	44.2
Cyclosporine	13.5	...
Endothelin	...	38.8
<b>Subtotal Phase III</b>	<b>144.4</b>	<b>173.3</b>
<b>Phase IV</b>		
Depakote	33.6	24.1
Gabitril	...	1.4
Hydrocodone	...	4.0
Clarithromycin	23.4	14.9
Omnicef	...	4.9
Fenofibrate	2.2	1.4
Ritonavir	10.1	4.0
Kaletra	...	6.8
Cyclosporine	...	2.5
<b>Subtotal Phase IV</b>	<b>69.3</b>	<b>64.0</b>
<b>Other</b>		
Discovery	190.6	192.0
Global Other	34.4	86.1
<b>Subtotal Other</b>	<b>225.0</b>	<b>278.1</b>
<b>Affordability</b>	...	(9.8)

**Global Pharmaceutical Research & Development  
Funding by Phase  
2001 PLAN**

\*Excluding Sister Divisions

GROUP/Phase/Expense by Phase 01 PLAN/Sheet1

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# ***Target Detail/ Book Pages to PPD***

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ABBT 0037562

**2001 PLAN**  
**Global Pharmaceutical Research & Development**  
**R&D/Medical Expenses Summary**  
**(\$000)**

	2000 Actual	2000 AGU	2001 PLAN	2001 PLAN Fav/(Unfav) vs 2000 AGU	Memo: Global R&D
Discovery	190,618	184,750	192,000	(7,250)	192,000
Global Development	313,302	318,565	328,307	(9,742) (A)	328,307
Domestic Development	55,441	55,183	51,729	3,454	
Gross PPD	559,361	558,498	572,036	(13,538)	520,307
TAP and Sister Division	65,275	67,809	57,348	10,461	
Total Gross Expense	624,636	626,307	629,384	(3,077)	
Net PPD	375,593	374,730	385,367	(10,637)	208,124
Expense by Classification:					
Salaries/Fringe/Contract	204,133	207,042	222,483	(15,441)	
Travel/Meetings	8,452	7,800	8,327	(527)	
Other Employee Related	9,274	8,999	9,901	(902)	
MIS	5,074	5,074	5,074	...	
Corp Allocation	21,869	21,894	22,924	(1,030)	
Other	375,834	378,140	370,439	8,701 (A)	
Affordability	...	(3,642)	(9,764)	6,122	
Total Expense	624,636	626,307	629,384	(3,077)	

**Commentary:**

(A) Primarily due to increased support for Quinolone, Ketolide and Endothelin.

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 ARRT 0037563

**2001 PLAN (FINAL)  
PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT  
GLOBAL/DOMESTIC SPLIT  
(\$MM)**

	Actuals through 2000		2000 AGU		2001 PLAN		PLAN vs AGU FAV/(UNF)	
	GROSS	PPD	GROSS	PPD	GROSS	PPD	GROSS	PPD
<b>FRANCHISES</b>								
<b>NEUROLOGY</b>								
Depakote	179.9	179.9	30.4	30.4	24.1	24.1	6.3	6.3
Gabrilin	136.5	122.9	2.0	1.8	1.4	1.3	0.6	0.5
ABT-594 (formerly CCM)	62.2	37.3	14.4	8.6	9.3	5.5	5.1	3.0 (A)
COX-II	2.7	1.6	4.0	2.4	1.2	0.7	2.8	1.7
ABT-089 (formerly ChCM)	1.6	1.0	3.0	1.8	0.6	0.4	2.4	1.4
ABS-103	...	...	...	...	...	...	...	...
NPS-1776	...	...	...	...	...	...	...	...
RP Scherer / Alza (Hydrocodone)	...	...	...	...	4.0	4.0	(4.0)	(4.0)
<b>Subtotal NEUROLOGY</b>	<b>382.9</b>	<b>342.7</b>	<b>53.8</b>	<b>45.0</b>	<b>40.6</b>	<b>36.1</b>	<b>13.2</b>	<b>8.9</b>
<b>ANTI-INFECTIVE</b>								
Clarithromycin	383.8	236.3	26.4	15.8	14.9	8.9	11.5	6.9
Kelotide	153.8	92.3	74.1	44.5	88.0	52.8	(13.9)	(8.3) (C)
Ketolide Task	...	...	(7.0)	(4.2)	...	...	(7.0)	(4.2)
Quinolone	11.6	7.0	6.8	4.1	24.5	14.7	(17.7)	(10.6) (D)
Neuraminidase	...	...	2.5	1.5	...	...	2.5	1.5
Omnicef	...	...	...	...	4.9	4.9	(4.9)	(4.9)
<b>Subtotal ANTI-INFECTIVE</b>	<b>669.2</b>	<b>335.6</b>	<b>102.8</b>	<b>61.7</b>	<b>132.3</b>	<b>81.3</b>	<b>(25.6)</b>	<b>(19.6)</b>
<b>UROLOGY/CARDIOLOGY</b>								
BPH Backup	85.7	51.4	34.0	20.4	2.3	1.4	31.7	19.0 (B)
Fenofibrate (Fournier)	14.1	14.1	1.0	1.0	1.4	1.4	(0.4)	(0.4)
Nippon Shinyaku (NS49)	12.3	7.4	2.7	2.2	...	...	2.7	2.2
KCO	...	...	...	...	5.0	4.0	(5.0)	(4.0)
<b>Subtotal UROLOGY/CARDIOLOGY</b>	<b>112.1</b>	<b>72.9</b>	<b>37.7</b>	<b>23.6</b>	<b>8.7</b>	<b>6.8</b>	<b>29.0</b>	<b>16.8</b>
<b>HIV</b>								
Ritonavir	299.3	178.6	13.0	7.8	4.0	2.4	9.0	5.4
Kaletra	215.7	129.4	78.5	46.7	51.0	30.6	25.5	16.1 (E)
Cyclosporine	61.0	36.6	11.7	8.4	2.5	1.5	9.2	6.9
<b>Subtotal HIV</b>	<b>576.0</b>	<b>345.6</b>	<b>101.2</b>	<b>62.9</b>	<b>57.5</b>	<b>34.5</b>	<b>43.7</b>	<b>28.4</b>
<b>CANCER</b>								
Endothelin	96.4	57.8	13.0	7.8	38.8	23.3	(25.8)	(15.5) (C)
TSP #1	11.0	6.6	6.6	4.0	10.0	6.0	(3.4)	(2.0)
Metalloproteinase	5.6	3.4	5.0	3.0	7.4	4.4	(2.4)	(1.4)
Ani-Mitotic	3.9	2.3	6.0	4.8	8.4	5.0	(2.4)	(0.2)
K-5	1.0	0.6	1.0	0.6	...	...	1.0	0.6
FTI #2	...	...	...	...	...	...	...	...
<b>Subtotal CANCER</b>	<b>117.9</b>	<b>70.7</b>	<b>31.6</b>	<b>20.2</b>	<b>64.8</b>	<b>38.7</b>	<b>(33.0)</b>	<b>(18.5)</b>
<b>Other New Products</b>								
Other	n/a	n/a	50.3	52.6	...	...	...	...
Affordability	n/a	n/a	(3.8)	(2.2)	(9.8)	(5.9)	(6.2)	3.7
<b>Total Development</b>	<b>n/a</b>	<b>n/a</b>	<b>373.8</b>	<b>283.8</b>	<b>380.0</b>	<b>270.2</b>	<b>(8.3)</b>	<b>(6.4)</b>
Discovery	n/a	n/a	184.8	110.9	192.0	115.2	(7.3)	(4.3)
<b>Total Gross/Net PPD</b>	<b>n/a</b>	<b>n/a</b>	<b>559.5</b>	<b>374.7</b>	<b>572.0</b>	<b>385.4</b>	<b>(13.5)</b>	<b>(10.7)</b>

**Commentary:**

- (A) Funding assumes No Go decision at 2Q 2001 decision point  
 (B) BPH Backup project was killed 10/00 and reflects shut down expenses in 2001  
 (C) Reflects higher costs associated with Phase III  
 (D) Reflects higher costs associated with Phase II  
 (E) Decrease reflects year 2000 launch

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**PHARMACEUTICAL PRODUCTS RESEARCH & DEVELOPMENT  
GLOBAL A/SPLIT  
(\$MILLIONS)**

	2000 PLAN		2001 PLAN	
	Global	Domestic	Global	Domestic
<b>NEUROLOGY</b>				
Depakote	...	32.7	...	24.1
Gabirin	0.5	1.5	...	1.4
ABT-594 (formerly CCM)	15.0	...	9.3	...
Cox-II	...	...	1.2	...
ABT-089 (formerly ChCM)	...	...	0.6	...
ABS-103	...	...	...	...
NPS-1776	...	...	...	...
RP Scherer / Alza (Hydrocodone)	15.5	34.2	11.1	4.0
				29.5
<b>ANTI INFECTIVE</b>				
Claritromycin	27.0	...	14.9	...
Kenolide	71.3	...	88.0	...
Quinolone	14.0	...	24.5	...
Neuraminidase	5.8	...	...	...
Onnitof	...	...	...	4.9
	118.1	...	127.4	4.9
<b>UROLOGY/CARDIOLOGY</b>				
BPH Backup	38.0	...	2.3	...
Tritor (Fenofibrate)	...	2.0	...	1.4
Nippon Shinyaku (NS-49)	5.2	5.2	...	...
KCO	...	...	5.0	...
	43.2	7.2	7.3	1.4
<b>HIV</b>				
Ritonavir	13.0	...	4.0	...
Kaletra	74.6	...	51.0	...
Cyclosporine	7.9	4.1	2.5	...
	95.5	4.1	57.5	...
<b>CANCER</b>				
Endothelin	6.0	...	38.8	...
Metalloproteinase (MMP)	5.0	...	7.4	...
Farnesyltransferase (FTI) #2	3.8	...	...	...
TSP #1	5.0	...	10.0	...
TSP #2	1.0	...	...	...
Anti-Mitotic	5.0	...	8.4	...
K5	...	...	...	...
	25.8	...	64.6	...
<b>Other New Products</b>	7.2	...	...	...
<b>Other</b>	52.5	16.1	68.9	17.2
	...	...	...	...
<b>Total Development</b>	<b>357.8</b>	<b>61.6</b>	<b>336.8</b>	<b>53.0</b>
<b>Discovery</b>	185.0	...	192.0	...
	...	...	...	...
<b>Total PPD (Without Risk)</b>	<b>542.8</b>	<b>61.6</b>	<b>528.8</b>	<b>53.0</b>
<b>Risk/Affordability</b>	(45.7)	(5.3)	(6.5)	(1.3)
<b>Total PPD (With Risk)</b>	<b>497.1</b>	<b>56.3</b>	<b>520.3</b>	<b>51.7</b>
<b>TOTAL GLOBAL PPD (With Risk)</b>	<b>542.8</b>	<b>61.6</b>	<b>528.8</b>	<b>53.0</b>
<b>TOTAL GLOBAL PPD (Without Risk)</b>	<b>598.5</b>	<b>66.9</b>	<b>584.8</b>	<b>54.3</b>
<b>2000 PLAN</b>	<b>598.5</b>	<b>66.9</b>	<b>584.8</b>	<b>54.3</b>
<b>2001 PLAN</b>	<b>584.8</b>	<b>54.3</b>	<b>542.8</b>	<b>53.0</b>
<b>AI Split as Calculated @ 40%</b>	191.8	...	208.1	...
<b>AI Split per IDV</b>	183.8	...	186.7	...
<b>Under/Over Charge</b>	15.0	...	21.4	...

Book II IDV was \$198,670  
Per Jeff McGuire A.I. will pay \$12,000 less  
\$198,670 - \$12,000 = \$186,670  
208,120 - 186,670 = 21,450 A.I. Undercharge

Note: r-UCB-Pro-UCB/Absorbance transfer to HFD reflected

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## PHARMACEUTICAL PRODUCTS RESEARCH &amp; DEVELOPMENT

	Corporate Submission	Final 2001 PLAN	Final vs. Corp Sub Inc/(Dec)
<b>NEUROSCIENCE</b>			
Depakote	26.0	24.1	(1.9)
Gabitril	...	1.4	1.4
ABT-594	8.9	9.3	0.4
COX - II	3.0	1.2	(1.8)
ABT-089	7.0	0.6	(6.4)
ABS-103	3.3	...	(3.3)
NPS-1778	3.7	...	(3.7)
RP Scherer / Alza	4.0	4.0	...
Subtotal NEUROLOGY	55.9	40.6	(15.3)
<b>ANTI INFECTIVE</b>			
Clarithromycin	20.0	14.9	(5.1)
Ketolide	91.0	88.0	(3.0)
Quinolone	25.0	24.5	(0.5)
Neuraminidase	...	...	...
Omnicef	5.0	4.9	(0.1)
Subtotal ANTI INFECTIVE	141.0	132.3	(8.7)
<b>UROLOGY/CARDIOLOGY</b>			
BPH Backup	25.4	2.3	(23.1)
Fenofibrate (Fournier)	4.0	1.4	(2.6)
Nippon Shinyaku (NS49)	...	...	...
KCO	6.0	5.0	(1.0)
Subtotal UROLOGY/CARDIOLOGY	35.4	8.7	(26.7)
<b>HIV</b>			
Ritonavir	4.0	4.0	...
Kaletra	41.5	51.0	9.5
Cyclosporine	2.0	2.5	0.5
Subtotal HIV	47.5	57.5	10.0
<b>CANCER</b>			
Endothelin	23.0	38.8	15.8
TSP #1	9.0	10.0	1.0
Metalloproteinase	7.0	7.4	0.4
Anti-Mitotic	10.0	8.4	(1.6)
K-5	8.8	...	(8.8)
FTI #2	4.1	...	(4.1)
Subtotal CANCER	61.9	64.6	2.7
<b>Other New Products</b>			
Other	78.5	86.1	7.6
Affordability	(25.1)	(9.8)	15.3
Total Development	395.1	380.0	(15.1)
Discovery	197.0	192.0	(5.0)
Total Gross PPD	592.1	572.0	(20.1)
TAP & Sister Division	59.2	57.4	(1.8)
Total Gross	651.3	629.4	(21.9)

LORD/PHARMA Confidential - Summary 91\_11\_01\_01 Project Numbers

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**Pharmaceutical Products Division - R&D  
Summary of R&D Projects  
2001 PLAN**

Project/Description	Cost thru 2000	2000 Actual	2001 PLAN	Cost until NDA 2002 and Forward
<b>Depakote</b> Development programs to enhance the Depakote/Depacon product position in the treatment of epilepsy, prevention of migraine headaches and the treatment of manic episodes associated with bipolar disorder. This includes a new extended release formulation in each of these treatment areas and studies to expand the market for treating impulsive aggression, psychosis, elderly agitation, a comparator study with Lilly's anti-psychotic drug, Zyprexa, and bipolar in pediatric mania. Additionally, the Depacon Rapid Infusion Study will assess the safety of rapidly loading Depacon in patients with Epilepsy. Two new formulations are being developed - 250 mg ER tablet and DR Spinning Disk.	\$179.9	\$33.6	\$24.1	N/A
<b>ABT-594</b> [Milestone: Go/No Go Clinical Efficacy, 2Q01, NDA Date: 3Q03] ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator. It is effective across all pain conditions; nociceptive pain and neuropathic pain. Preclinical data shows ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in treating moderate to severe pain in several well characterized animal models of nociceptive pain. ABT-594 has a unique mechanism of action which may encourage use in combination with other analgesics as well as monotherapy. Indicated for the management of neuropathic pain associated with diabetic polyneuropathy. Indication or publication for specific chronic nociceptive and/or neuroreceptive pain condition (e.g., OA). Oral formulation expected. Dosing schedule to be determined.	\$62.2	\$14.3	\$9.3	\$71.0
<b>ABT-089</b> [Milestone: Transition Team Go/No Go, 4Q01] ABT-089 is a potent and selective neuronal nicotinic receptor modulator with cognition enhancing activity in rodent and primate preclinical models of cognitive dysfunction. It does not appear to have nicotine like dependence liability or abuse. ABT-089 may be the second non-scheduled, non-stimulant product for the ADHD market. Oral formulation and QD dosing expected.	\$1.6	\$1.6	\$0.6	\$102.3
<b>Clarithromycin</b> The NDA for clarithromycin extended release (Biaxin XL) was approved March 3, 2000. New studies planned for the U.S. include Asthma and Cystic Fibrosis. International Projects for 2001 include OD XL registration studies and the Japan 400mg tablet.	\$393.8	\$23.5	\$14.9	N/A
<b>Ketolide (ABT-773)</b> [Milestone: Phase III CAP/AMS dose range data 2Q01, Tablet NDA 3Q02] ABT-773 is a potent ketolide with strong activity against most macrolide resistant strains while also maintaining the broad spectrum coverage of clarithromycin. Product will be available as tablet followed by a pediatric suspension and injectable form dependent on timing of funding. ABT-773 will address the major unmet medical needs of increasing resistance to current empiric agents and weak activity against key problem pathogens, especially <i>S. pneumoniae</i> . Maintains clarit's claim of "Spans the spectrum" (G+, G-, atypicals). Cover key O+ resistant strains ( <i>S. pneumoniae</i> , <i>S. pyogenes</i> ). Tablet dosing will be QD or BID based on severity of indications. Five days for ABCEB, Pharyngitis, 10 days for AMS and CAP. COGS no more than \$2,500/kg at launch. Pediatric and IV currently not funded.	\$153.8 (Tab)	\$74.5 (Tab)	\$88.0 (Tab)	\$42.0 (Tab US/EU)
<b>Quinolone (ABT-492)</b> [Milestone: Go/No Go PK/Safety (Phase Ia) 2Q01, NDA Date: 4Q04] ABT-492 is a broad-spectrum anti-infective agent with potential application across a range of indications, including respiratory infections, genitourinary infections, and skin/soft tissue infections. Product will initially be available as tablet/capsule followed by an injectable form approximately one year later. The in vitro antibacterial activity of ABT-492 appears to be more potent than trovafloxacin. The in vitro potency data suggested that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin. Must have a safety profile comparable to levofloxacin. QD dosing for adult tablets/capsule and IV. Five days for most indications.	\$11.6	\$7.1	\$24.5	\$227.6 (Tab)
<b>Omnicef</b> [Milestone: Initiate Clinical Studies 3Q01, SNDA Q402] Cefdinir (Omnicef) is a potent cephalosporin indicated for the full range of respiratory tract and skin infections, and has 5 day BID indications for AOM, pharyngitis, and AECB. The suspension is pleasant tasting; significantly better than Cefzil and Augmentin in 2 studies, and better than Zithromax in 1 of 2 studies. A new study will pursue claims for 5 day, once daily dosing in AOM, and generate comparative data vs. Zithromax with both once daily and twice daily dosing. A second study is planned for AECB and is currently Blue Plan. Comparator agents are under evaluation. The NDA would be filed Dec 2002.	\$0.0	\$0.0	\$4.9	N/A
<b>Benign Prostatic Hyperplasia Back-up (ABT-980)</b> [Program terminated 10/00] ABT-980 is a potent @1a selective adrenoceptor antagonist with 130-fold selectivity for @1a versus @1b receptor in the medical treatment of benign prostatic hyperplasia. Indicated for the relief of symptomatic benign prostatic hyperplasia. <i>ABT-980 program had to be terminated in 10/00 due to the development of serum transaminase abnormalities in patients.</i>	\$85.7	\$31.5	\$2.3	\$0.0

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**Pharmaceutical Products Division - R&D  
Summary of R&D Projects  
2001 PLAN**

Project/Description	Cost thru 2000	2000 Actual	2001 PLAN	Cost until NDA 2002 and Forward
<b>Kaletra</b> ABT-378 is a second generation protease inhibitor which will be coformulated in one capsule/tablet with ritonavir. It is potent against purified HIV protease with a Ki of 1pM. Phase I studies indicate that ABT-378 is safe and well tolerated at all doses studied. ABT-378 works only in combination with ritonavir. Ritonavir acts as a potent binder of the P450 system to enhance the PK profile of ABT-378 to achieve higher blood levels than on its own. Indicated as first-line protease inhibitor therapy in adults. Efficacy against resistant virus. Must maintain high plasma and tissue concentrations. Safety, side effect, and toxicity profile at least equal to current standard. Dosing: BID, QD possible. Will be available in one coformulated pill with ritonavir.	\$215.7	\$80.8	\$51.0	N/A
<b>Endothelin (ABT-627)</b> [Milestone: Initiate Phase III Clinicals 1Q01] ABT-627 is Abbott's leading endothelin antagonist receptor. ABT-627 is seeking an indication for the treatment of hormone refractory prostate cancer. ABT-627 is orally administered and well tolerated as chronic therapy. It has demonstrated improvement of time to disease progression compared to placebo. It has also demonstrated improvement in time to PSA progression compared to placebo.	\$96.4	\$16.8	\$38.8	\$51.0
<b>TSP #1 (ABT-510)</b> [Milestone: Go/No Go Clinical Safety, 2Q01] ABT-510 is a parenteral thrombospondin mimetic. TSP is an angiogenesis inhibitor that may prevent growth of primary tumors as well as prevent the spread of metastases by inhibiting the growth of collateral vessels required to provide blood to growing tumors. With a relatively benign toxicity profile, this class of agents may be used to prevent metastatic disease in patients who have received surgery, radiation or chemo and/or as primary therapy to treat cancer patients. As chronic, long-term therapy, there is potential for significant commercial opportunity.	\$11.0	\$7.0	\$10.0	\$80.5
<b>Metalloproteinase (MMPI) (ABT-518)</b> [Milestone: Go/No Go Clinical Safety, 4Q01] ABT-518 is an oral, matrix metalloproteinase inhibitor and a cytostatic agent. MMPI's may prevent the growth of metastatic lesions and inhibit primary tumor growth. These agents will most likely be used with current therapy or post-definitive therapy such as surgery, radiation and chemotherapy. As chronic, long-term therapy, there is significant commercial upside.	\$5.6	\$5.6	\$7.4	\$86.3
<b>Anti-Mitotic (Elsat) (ABT-751)</b> [Milestone: Go/No Go Clinical Safety, 2Q01] ABT-751 is an oral cytotoxic agent that inhibits tumor growth by inhibiting the polymerization of tubulin into microtubules, a necessary step in cell division. This mechanism of action is somewhat similar to the mechanism of taxanes. This novel agent could produce clinical benefits equal to or superior to current taxanes and could be as commercially successful as current taxanes. ABT-751 also has the potential to be effective in patients experiencing resistance to other agents, including taxanes.	\$3.9	\$3.9	\$8.4	\$78.0
<b>Other</b> Other projects include Gabitril, COX-II, ABS-103, NPS-1776, Hydrocodone, Fenofibrate, KCO, Ritonavir, Cyclosporine, CAPD Excess Capacity Charges, and CAPD Clari process improvements.	N/A	\$68.6	\$105.6	N/A
<b>Affordability</b> Reflects Risk.	N/A	\$0.0	(\$9.8)	N/A
<b>Discovery</b> Funding provides for five Discovery Development Candidates (DDCs) to be brought forth in 2001. Reflects Discovery costs in Infectious Disease Research, Metabolic Disease Research, Neurological and Urological Disease Research, and Cancer Research. Includes Neurosearch, Karo Bio, ICAGEN, IDUN, Incyte and ISIS collaborations.	N/A	\$190.6	\$192.0	N/A
<b>Total Gross PPD</b>	N/A	\$559.4	\$572.0	N/A

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ABBT 0037569

2001 PLAN SUMMARY  
11/01/1997



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Pharmaceutical Products Division R&D  
Plan Galling Rollforward  
Gross Expense

	January	February	March	April	May	June	July	August	September	October	November	December	TOTAL
<b>Reductions</b>													
Other Functional Expense	(2,054)	(1,923)	(2,020)	(1,980)	(1,949)	(2,116)	(2,108)	(2,175)	(2,101)	(2,038)	(2,033)	(2,243)	(24,800)
BPH Grants	100	100	100	(1,269)	(1,184)	(683)	(1,489)	(1,489)	(1,307)	(1,350)	(1,307)	(1,309)	(11,416)
CCM Grants	(267)	(267)	(267)	(516)	(516)	(516)	(516)	(516)	(1,097)	(2,350)	(1,333)	(2,555)	(13,052)
Omniel Grants	0	0	0	0	0	0	0	0	0	(500)	(500)	(500)	(2,000)
All Other	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(75)	(800)
<b>Total Reductions</b>	<b>(2,296)</b>	<b>(2,168)</b>	<b>(2,262)</b>	<b>(3,840)</b>	<b>(3,724)</b>	<b>(3,816)</b>	<b>(4,188)</b>	<b>(4,351)</b>	<b>(5,123)</b>	<b>(6,408)</b>	<b>(7,248)</b>	<b>(8,392)</b>	<b>(82,188)</b>
<b>Additions</b>													
Other	342	342	342	342	342	342	342	342	342	342	342	342	4,104
SPD Purchases	375	375	375	375	375	375	375	375	375	375	375	375	4,500
<b>Total Additions</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>717</b>	<b>8,604</b>
<b>Change in Net Affordability (\$20.1 to \$25.1)</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>417</b>	<b>5,000</b>
<b>Adjustment</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>2,163</b>	<b>25,950</b>

<b>Reductions</b>													
Other Functional Expense	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(2,543)	(30,512)
BPH Grants	(1,855)	(1,855)	(1,434)	0	0	0	0	0	0	0	0	0	(5,262)
KCO Grants	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(60)	(720)
Chari Cystic Fibrosis Grants	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(196)	(2,352)
Chari Asthma Grants	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(187)	(2,200)
Chari International Grants	0	0	(350)	(350)	(350)	(350)	(350)	(350)	(350)	(350)	(350)	(350)	(1,827)
CHCN Grants	(318)	(318)	(318)	(318)	(318)	(318)	(318)	(318)	(317)	(317)	(317)	(317)	(3,813)
Miscellaneous Grant Reductions	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(416)
CHMS IDV Reduction	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(416)
CRO Reduction	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(37)	(447)
SPD Purchases	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(338)	(4,028)
Hydrocodone Release out of Stock Purchased	0	0	0	0	0	0	0	0	0	0	0	0	0
Chari Int. Manpower	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Total Reductions</b>	<b>(8,884)</b>	<b>(8,884)</b>	<b>(8,874)</b>	<b>(4,374)</b>	<b>(4,814)</b>	<b>(4,816)</b>	<b>(4,773)</b>	<b>(4,773)</b>	<b>(4,773)</b>	<b>(4,844)</b>	<b>(4,868)</b>	<b>(4,868)</b>	<b>(58,884)</b>
<b>Additions</b>													
Kelatis Grants	333	333	333	333	333	333	333	333	333	333	333	333	4,000
Endothelin Grants	33	33	33	33	33	33	33	33	33	33	33	33	400
Cyclosporine Deal w/ SPD Unreimbursed	0	0	0	0	0	0	0	0	0	0	0	0	0
Elimination of Sargol Credit	1	1	1	1	1	1	1	1	1	1	1	1	12
Fluoropase and Depreciation Adjustments	0	0	0	0	0	0	0	0	0	0	0	0	0
Gabril reimbursement from Commercial	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Total Additions</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>4,400</b>
<b>Change in Net Affordability (\$25.1 to \$3.3)</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>1,276</b>	<b>15,300</b>
<b>Adjustment</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>1,310</b>	<b>15,710</b>

Quarterly Galling

First Plan	160,305	163,251	152,421	151,407	629,384
% versus 2000 AGU	5.82%	-4.46%	-1.16%	2.55%	0.49%
Book #2	168,731	169,351	183,759	159,494	681,334
% versus 2000 AGU	11.17%	-0.89%	-0.30%	6.72%	4.00%
Book #1	165,585	170,702	187,437	170,244	693,968
% versus 2000 AGU	9.08%	-0.10%	2.09%	13.82%	6.01%
2000 AGU	151,777	170,870	184,215	149,445	656,307

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2/1/07 10:05

# ***Other Miscellaneous Schedules***

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Pharmaceutical Products Division R&D  
Plan Gating Rollforward  
Net Expense

	January	February	March	April	May	June	July	August	September	October	November	December	TOTAL
<b>Reductions</b>													
Other Functional Expense	(1,232)	(1,154)	(1,212)	(1,183)	(1,169)	(1,270)	(1,285)	(1,305)	(1,261)	(1,259)	(1,220)	(1,346)	(14,860)
BPH Grants	60	60	60	(761)	(710)	(591)	(893)	(893)	(810)	(810)	(784)	(785)	(8,850)
CCM Grants	(160)	(160)	(160)	(310)	(310)	(310)	(310)	(310)	(500)	(500)	(2,000)	(1,713)	(7,831)
Omitted Grants	0	0	0	0	0	0	0	0	(500)	(500)	(45)	(45)	(2,000)
All Other	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(45)	(540)
<b>Total Reductions</b>	<b>(1,278)</b>	<b>(1,259)</b>	<b>(1,357)</b>	<b>(2,304)</b>	<b>(2,234)</b>	<b>(2,206)</b>	<b>(2,613)</b>	<b>(2,653)</b>	<b>(3,274)</b>	<b>(4,046)</b>	<b>(4,046)</b>	<b>(4,389)</b>	<b>(32,101)</b>
<b>Additions</b>													
Other	205	205	205	205	205	205	205	205	205	205	205	205	2,462
SPD Purchase	225	225	225	225	225	225	225	225	225	225	225	225	2,700
<b>Total Additions</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>430</b>	<b>5,162</b>
<b>Change in Net Affordability (\$21.3 to \$15.3)</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>250</b>	<b>3,000</b>
<b>Adjustment</b>	<b>811</b>	<b>812</b>	<b>812</b>	<b>812</b>	<b>811</b>	<b>811</b>	<b>812</b>	<b>811</b>	<b>812</b>	<b>812</b>	<b>812</b>	<b>810</b>	<b>7,338</b>
<b>Reductions</b>													
Other Functional Expense	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(1,526)	(18,307)
BPH Grants	(1,119)	(1,178)	(860)	0	0	0	0	0	0	0	0	0	(3,157)
KCO Grants	(300)	(36)	(36)	(36)	(36)	(36)	(36)	(36)	(36)	(36)	(36)	(36)	(432)
Clari Cysto Fibrosis Grants	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(118)	(1,411)
Clari Asthma Grants	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(100)	(1,200)
Clari International Grants	0	0	(210)	(210)	(210)	(210)	(210)	(210)	(210)	(210)	(210)	(210)	(2,587)
CHCM Grants	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(191)	(2,287)
Miscellaneous Grant Reductions	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(34)	(410)
CHMS IDV Reduction	0	0	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(268)
CRO Rebates	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(268)
SPD Purchase	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(336)	(4,028)
Hydrocodone Release out of Spec. Purchased	0	0	0	0	0	0	0	0	0	0	0	0	(2,350)
Clari Int Vapower	0	0	0	0	0	0	0	0	0	0	0	0	(2,350)
<b>Total Reductions</b>	<b>(3,781)</b>	<b>(3,840)</b>	<b>(3,432)</b>	<b>(2,772)</b>	<b>(2,186)</b>	<b>(2,186)</b>	<b>(2,102)</b>	<b>(2,102)</b>	<b>(3,098)</b>	<b>(2,886)</b>	<b>(2,887)</b>	<b>(2,884)</b>	<b>(36,827)</b>
<b>Additions</b>													
Kalitra Grants	0	0	0	0	0	0	0	0	0	0	0	0	0
Endothelin Grants	200	200	200	200	200	200	200	200	200	200	200	200	2,400
Hydrocodone domestic not global	133	133	133	133	133	133	133	133	133	133	133	133	1,600
Cyclosporine Deal w/ SPD terminated	33	33	33	33	33	33	33	33	33	33	33	33	400
Elimination of Singstat Credit	0	0	0	0	0	0	0	0	0	0	0	0	0
Florespace and Depreciation Adjustments	1	1	1	1	1	1	1	1	1	1	1	1	12
Gabitril reimbursement from Commercial	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Total Additions</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>367</b>	<b>1,720</b>	<b>2,186</b>	<b>2,187</b>	<b>2,407</b>	<b>14,715</b>
<b>Change in Net Affordability (\$11.3 to \$5.9)</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,283</b>	<b>1,284</b>	<b>1,284</b>	<b>1,284</b>	<b>1,284</b>	<b>15,400</b>
<b>Adjustment</b>	<b>393</b>	<b>393</b>	<b>393</b>	<b>(224)</b>	<b>89</b>	<b>70</b>	<b>(81)</b>	<b>(80)</b>	<b>(93)</b>	<b>(628)</b>	<b>(628)</b>	<b>(681)</b>	<b>(1,257)</b>

	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Total
<b>Quantile Gating</b>					
Final Plan	99,072	100,246	93,652	93,385	386,357
% versus 2000 AGU	-0.38%	-8.80%	10.30%	16.05%	2.84%
<b>Book #2</b>					
% versus 2000 AGU	102,696	103,204	93,919	93,528	393,437
% versus 2000 AGU	4.31%	-8.86%	10.62%	16.22%	4.89%
<b>Book #1</b>					
% versus 2000 AGU	102,954	108,153	96,384	102,836	410,037
% versus 2000 AGU	4.46%	-4.27%	15.97%	27.54%	9.42%
<b>2000 AGU</b>	<b>96,448</b>	<b>110,900</b>	<b>84,908</b>	<b>80,478</b>	<b>374,730</b>

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## 2001 Project Funding by Phase

Franchise	Pre-Clinical	(\$MM)	Phase I	(\$MM)	Phase II	(\$MM)	Phase III	(\$MM)	Phase IV	(\$MM)	2000 AGU
Neuroscience	COX-II	1.8	ABT-089	6.4	CCM: Neuro	9.3	Hydrocodone	4.0	Depakote: Ongoing	24.1	53.8
	COX-II	1.2	ABT-089	0.6	CCM: Neuro Milestone	16.0			Depakote: New	2.0	
	ABS-103	1.3			CCM: Osteo	10.1			Incremental Depakote	6.0	
	NPS-1776	3.7							Gabitril	1.4	
	ABS-103	4.0									
Anti-Infective			Quino: Tablet	24.5	Keto: Tablet	88.0	Omni: Otitis Media	2.4	Clar: TBD	14.9	102.8
			Quino: Tablet	0.5	Keto: Japan Reg	3.0	Omni: AECB	2.5	Clar: Cystic Fibrosis	0.7	
Urology/Cardiology					Keto: IV Form	7.0	Omni: Pharyngitis	5.0	Clar: Asthma	2.4	
	KCO	5.0					Bimodol	11.7	Clar: International	2.0	37.7
HIV/Immunosence							BPH Backup	2.3	Fenc: Diabetics	1.4	
	Gengraf: PREFER	1.0							Fenc: Diabetics	2.6	14.3
Onology	Gengraf: Peds PK	1.0					Ritonavir: Combo	4.0	2nd Gen: Ph IV Sustiva	2.0	101.2
							2nd Gen: HIV, BID, Oral	32.0	2nd Gen: Ph IV Switch	3.0	
Other	MMPI	7.4	TSP-1	10.0			2nd Gen: Imp Form	4.0	Other 2nd Gen	8.0	
	K5	8.8	Anti-Mitotic	8.4			2nd Gen: Post Appr	2.0			
Other	FTI	4.1					Gengraf: Organ Rel G	2.5			
							2nd Gen: QD Program	17.0			
Other	DDC-1	5.0					Endo: Prostata Ca	37.8			31.6
	DDC-2	5.0					Endo: Breast Ca	1.0			
Other	Discovery	192.0					Endo: Early Pca	11.0			
	DDC-3	5.0					Endo: Exploratory	5.0			235.0
Other	DDC-4	5.0									
	DDC-5	5.0									
Other	DDC-6	5.0									
		(9.8)								(9.8)	
2001 Affordability		205.6		129.6		97.3		94.5		54.8	
2001 Total Funded		55.7		38.9		36.1		49.7		21.7	
2001 Total Unfunded		(3.6)								(3.6)	
2000 Affordability		201.4		72.0		124.1		77.0		558.5	
2000 AGU											

Key:	Funded	Unfunded
Green:		
Ped:		

\* All fixed costs in "other" arbitrarily placed in phase 1.  
 \*\* In-licensed compounds may vary in both franchise and phase.

**Pharmaceutical Products Research & Development  
R&D/Medical Expenses Summary  
(\$000)**

	1998 ACTUAL	1999 ACTUAL	2000 PLAN	2000 APU	2000 AGU	2001 PLAN
Global Discovery	162,565	170,792	185,000	185,000	184,750	192,000
Global Development	263,041	248,486	312,126	327,300	318,565	328,307
Subtotal Global	425,606	419,278	497,126	512,300	503,315	520,307
% growth vs. prior year		-5.5%	25.6%	4.9%	-2.7%	3.1%
A.I. \$ share	170,242	165,911	183,768	183,768	183,768	186,670
A.I. % share	40.0%	39.6%	37.0%	35.9%	36.5%	35.9%
A.I. % share growth		-2.5%	10.8%			1.6%
PPD \$ share	255,364	253,367	313,358	328,532	319,547	333,637
PPD % share	60.0%	60.4%	63.0%	64.1%	63.5%	64.1%
PPD % share growth		-0.8%	23.7%			6.5%
Domestic Development	66,861	63,876	56,290	55,183	55,183	51,729
Gross PPD	492,467	483,154	553,416	567,483	558,498	572,036
TAP and Sister Division	58,700	58,301	52,694	65,459	67,809	57,348
Total Gross Expense	551,167	541,455	606,110	632,942	626,307	629,384
Net PPD	322,225	315,443	369,648	383,815	374,730	385,367

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Detail of "Other"  
2001 PLAN

	Oracle			Adjustments			2001 PLAN			2000 AGU			Variance Fav/(Unfav)
	Global	Domestic	Total	Global	Domestic	Total	Global	Domestic	Total	Global	Domestic	Total	
<b>Misc PPD R&amp;D</b>													
Altemate Dosage	110	...	110	...	...	...	110	...	110	2,003	...	2,003	1,893
In Licensing	403	...	403	...	...	...	403	...	403	1,781	...	1,781	1,358
Exploratory Effort	468	...	468	...	...	...	468	...	468	925	...	925	457
Prescription for Growth	123	...	123	...	...	...	123	...	123	927	...	927	804
Bimoclomol	71	...	71	...	...	...	71	...	71	...	...	...	(71)
NS-48 ABT-232	57	...	57	...	...	...	57	...	57	...	...	...	(57)
Abbotkinase & Recombinant Pro-UK	...	38	38	...	...	...	...	38	38	...	...	...	(38)
Molecular Probes	...	...	...	7	...	7	7	...	7	7	...	7	...
Drug User Fees	...	...	...	1,207	...	1,207	...	1,207	1,207	...	1,951	1,951	744
Patent to Operations	...	...	...	...	...	...	...	...	...	...	200	200	200
Depr & Floorspace not in fund	...	...	...	3,168	...	3,168	3,168	...	3,168	2,289	...	2,289	(697)
Inventory Transfer ABT 378	...	...	...	...	...	...	...	...	...	(5,728)	...	(5,728)	(5,728)
Clinical Supplies (Operations)	...	...	...	200	...	200	200	...	200	200	...	200	...
Comdisco	...	...	...	...	...	...	...	...	...	2,440	...	2,440	2,440
SDG/Other	...	...	...	...	...	...	...	...	...	1,500	...	1,500	1,500
IT Productivity Projects	...	...	...	...	...	...	...	...	...	...	...	...	...
Knoll/HIV/QD/Other	...	...	...	...	...	...	...	...	...	1,000	...	1,000	1,000
Genset #1	...	...	...	...	...	...	...	...	...	500	...	500	500
Genset #2	...	...	...	...	...	...	...	...	...	...	...	...	...
Coaction	...	...	...	...	...	...	...	...	...	...	...	...	...
CI charge from Ops (Cin Val Mgr)	...	...	...	...	...	...	...	...	...	171	...	171	171
SPD IDV - Liponair	...	...	...	...	...	...	...	...	...	607	...	607	607
Aegle Insurance	...	...	...	...	...	...	...	...	...	952	...	952	952
Data Management Absorption	...	...	...	...	...	...	...	...	...	1,078	...	1,078	1,078
Other New Products	...	...	...	...	...	...	...	...	...	2,850	...	2,850	2,850
AI Manpower	...	...	...	...	...	...	...	...	...	148	...	148	148
	1,232	38	1,270	3,373	1,207	4,580	4,605	1,245	5,850	13,412	2,151	15,563	9,713
<b>Non-Promoted Products</b>													
Clari	...	2,480	2,480	...	...	...	...	2,480	2,480	...	2,480	2,480	...
MHC	...	2,568	2,568	...	...	...	...	2,568	2,568	...	858	858	(1,710)
New Candidates	...	...	...	...	...	...	...	...	...	...	...	...	...
All Other (Detail Below)	93	8,073	8,166	...	...	...	93	8,073	8,166	1,582	10,691	12,283	4,117
	93	13,121	13,214	...	...	...	93	13,121	13,214	1,582	14,029	15,621	2,407
<b>SPD Misc</b>													
Outsourcing	...	...	...	...	...	...	...	...	...	552	...	552	552
Purchasing Abbot/Other	...	...	...	...	...	...	...	...	...	...	...	...	...
Hazards Lab	...	...	...	...	...	...	...	...	...	...	...	...	...
	...	...	...	...	...	...	...	...	...	552	...	552	552
<b>SPD Process</b>													
Unit of Activity Charge	23	...	23	...	...	...	23	...	23	28	...	28	5
Ery A for Clari Improve	...	369	369	...	...	...	...	369	369	...	838	639	270
Clari Process Improve	1,973	...	1,973	...	...	...	1,973	...	1,973	2,507	...	2,507	534
H2G	...	...	...	...	...	...	...	...	...	...	...	...	...
New Project Support	7,152	...	7,152	...	...	...	7,152	...	7,152	...	...	...	(7,152)
Disc - Delivery	...	...	...	...	...	...	...	...	...	...	...	...	...
Discovery Patents & Trademarks	370	...	370	...	...	...	370	...	370	...	...	...	(370)
Fixed Cost to SPD (PARD)	...	...	...	...	...	...	...	...	...	...	...	...	...
Protease 2nd Gen (Mfg Chg)	...	...	...	...	...	...	...	...	...	5,728	...	5,728	5,728
Clari IV	4,297	...	4,297	...	...	...	4,297	...	4,297	4,700	...	4,700	403
H2G - Fixed NCPP	...	...	...	...	...	...	...	...	...	...	...	...	...
Angiogenesis - Fixed NCPP	...	...	...	...	...	...	...	...	...	...	...	...	...
Miscellaneous Adjustment	...	...	...	...	...	...	...	...	...	151	...	151	151
	13,815	369	14,184	...	...	...	13,815	369	14,184	13,112	638	13,751	(433)
<b>Excess Capacity - SPD</b>													
PPD R&D Key Consol	11,610	...	11,610	...	...	...	11,610	...	11,610	9,180	...	9,180	(2,450)
PPD R&D Suspense	...	...	...	...	...	...	...	...	...	...	...	...	...
Corp Key Consol	...	...	...	...	...	...	...	...	...	...	...	...	...
Mfg Suspense	...	...	...	...	...	...	...	...	...	...	...	...	...
	11,610	...	11,610	...	...	...	11,610	...	11,610	9,180	...	9,180	(2,450)
<b>Excess Capacity - PPD</b>													
Discovery	...	...	...	...	...	...	...	...	...	332	25	357	357
Drug Safety	...	...	...	...	...	...	...	...	...	834	...	834	834
Development Ops	...	...	...	...	...	...	...	...	...	35	...	35	35
Venture Management (Thrombo)	...	...	...	...	...	...	...	...	...	...	...	...	...
Venture Mgmt	...	...	...	...	...	...	...	...	...	...	1,162	1,162	1,162
PARD	...	...	...	...	...	...	...	...	...	...	59	59	59
Data Management (Sale overstated)	...	...	...	...	...	...	...	...	...	2,000	...	2,000	2,000
	...	...	...	...	...	...	...	...	...	3,201	1,246	4,447	4,447
<b>Other Miscellaneous Credits</b>													
CRO Rebates	...	...	...	(3,000)	...	(3,000)	(3,000)	...	(3,000)	...	...	...	3,000
Navo Settlement	...	...	...	...	...	...	...	...	...	(1,500)	...	(1,500)	(1,500)
FLAP/Vanguard	...	...	...	...	...	...	...	...	...	(818)	...	(818)	(818)
Triangle Payments	...	...	...	...	...	...	...	...	...	2,914	...	2,914	2,914
Sangstat (Cyclosporine)	...	...	...	...	...	...	...	...	...	2,400	...	2,400	2,400
Metabolix	...	...	...	...	...	...	...	...	...	(888)	...	(888)	(888)
All Other	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>Subtotal OTHER</b>	26,750	13,528	40,278	373	1,207	1,580	27,123	14,735	41,858	43,137	18,065	61,202	18,344
Absorption/Unidentified	...	...	...	...	...	...	41,777	2,465	44,282	...	...	...	(41,942)
<b>TOTAL "OTHER"</b>	...	...	...	...	...	...	68,900	17,220	86,120	45,457	18,065	63,522	(22,598)
-- Should be equal.													
Blue Text = Inputs													
<b>All Other</b>													
Hytrin	66	275	341	...	...	...	66	275	341	62	275	357	16
Macrolide ABT797	...	...	...	...	...	...	...	...	...	25	...	25	25
Prokinetic Macrolide ABT229	...	...	...	...	...	...	...	...	...	18	...	18	18
H2G ABT608	5	...	5	...	...	...	5	...	5	97	...	97	92
Taxane ABT271	...	...	...	...	...	...	...	...	...	14	...	14	14
FLAP ABT080	22	...	22	...	...	...	22	...	22	114	...	114	92
Bimoclomol ABT822	...	...	...	...	...	...	...	...	...	1,242	...	1,242	1,242
Discovery	...	...	...	...	...	...	...	...	...	...	...	...	...
IMAT	...	...	...	...	...	...	...	...	...	...	...	...	...
HAART Metabolic Complications	...	...	...	...	...	...	...	...	...	...	...	...	...
Misc	...	...	...	...	...	...	...	...	...	...	...	...	...
Fenofibrate (Vascular)	...	...	...	...	...	...	...	...	...	96	...	96	96
Compliance Initiative	...	8,097	8,097	...	...	...	...	8,097	8,097	...	6,279	6,279	182
Pharmacogenetics	...	1,701	1,701	...	...	...	...	1,701	1,701	...	4,041	4,041	2,340
<b>Total All Other</b>	93	8,073	8,166	...	...	...	93	8,073	8,166	1,582	10,691	12,283	4,117

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## 2001 PLAN Rollforward

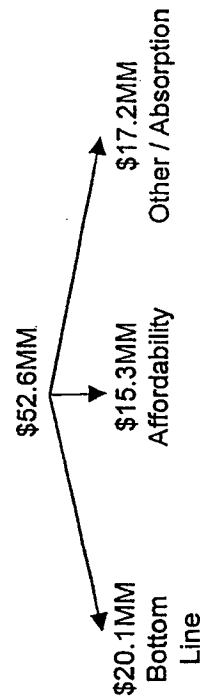
	Bottom Line	Other	Affordability
Book II	592.1	71.5	(25.1)
Re-prioritization	0	9.4 A	(2.6) B
Subtotal	<u>592.1</u>	<u>80.9</u>	<u>(27.7)</u>
Task Exercise	20.1	5.2 C	17.9 D
Final Plan	<u>572.0</u>	<u>86.1</u>	<u>(9.8)</u>

A Added \$12MM in grants and cut \$18.8MM in other. Projects cut (\$6.8MM) and functionals added \$2.6MM. This means absorption went up \$9.4MM.

B Functional impact was up \$12MM in grants and down (\$18.8MM / 2) = (\$9.4MM) in functionals \$12MM - \$9.4MM = \$2.6MM

C Projects cut \$55.0MM which translated into functional cuts of \$40.3MM. \$55.0MM - \$40.3MM = \$14.7MM of unabsorption. In addition to the unabsorption, relief was given by Commercial for Gabitril/Corp. Alloc for \$1.6MM, the Cyclosporine deal with SPD was terminated for an \$0.4MM, FTI #2 switch to KCO for (\$0.4MM), a change in the CMIS IDV for (\$0.4MM), elimination of Ketolide task 7.0MM, elimination of International Clari. charges for \$3.9MM, absorption changes of (\$13.1MM) and a change in affordability of (\$8.5MM).

D Of the \$40.3MM in functional cuts, we took \$20.1MM to the bottom line, therefore \$17.9MM went to reduce affordability



# ***Task Backup/ Rollforwards***

HIGHLY

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ADDT 0027577



**2001 Plan Task Exercise  
Pharmaceutical Products Division  
Research and Development  
(\$MM)**

Project Name	Project \$MM			Functional \$MM		
	Grants	Other	Total	Grants	Other	Total
- ABS/NPS	-	7.0	7.0	-	3.5	3.5
- Ketolide	-	5.0	5.0	-	2.5	2.5
- BPH	6.4	19.0	25.4	6.4	9.5	15.9
- Kaletra	(7.8)	(1.6)	(9.4)	(7.8)	(0.8)	(8.6)
- Endothelin	(10.6)	(5.6)	(16.2)	(10.6)	(2.8)	(13.4)
- KCO	0.5	5.5	6.0	0.5	2.8	3.3
- Depakote New Formulations	-	1.9	1.9	-	1.0	1.0
- K5	-	8.8	8.8	-	4.4	4.4
- Cox II	-	3.0	3.0	-	1.5	1.5
- Clarithromycin: Cystic Fibrosis Asthma International	0.7 2.4 2.0	- - -	0.7 2.4 2.0	0.7 2.4 2.0	- - -	0.7 2.4 2.0
- Tricor - Diabetics	-	4.0	4.0	-	2.0	2.0
- ChCM	1.6	5.4	7.0	1.6	2.7	4.3
- Discovery	-	5.0	5.0	-	5.0	5.0
- IM&T	-	-	-	-	1.0	1.0
- Project Expense	-	-	-	-	1.0	1.0
<b>Total Task</b>	<b>(4.8)</b>	<b>57.4</b>	<b>52.6</b>	<b>(4.8)</b>	<b>33.2</b>	<b>28.4</b>

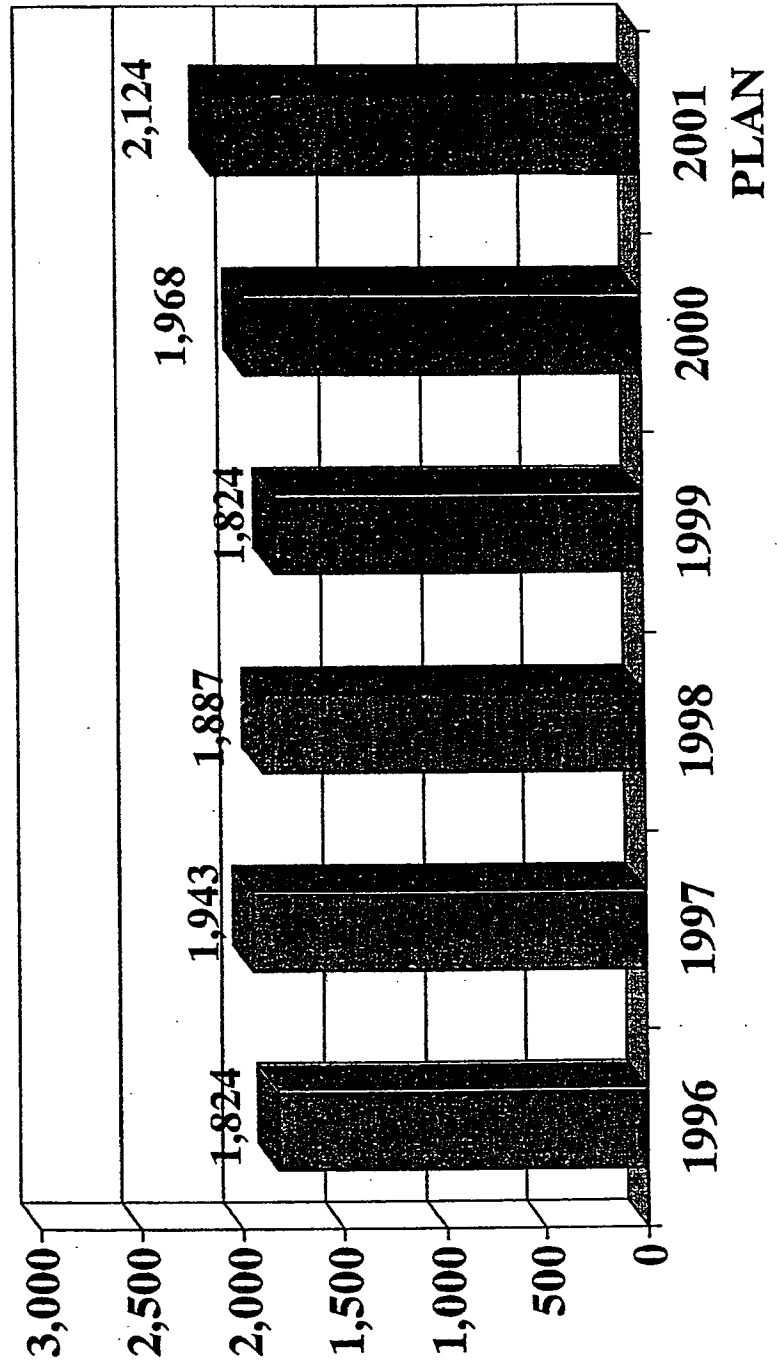
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# ***Headcount***

# R&D Regular Headcount 1996-2001



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ARRT 0037580

2001 PLAN  
Final PLAN vs AGU  
YEAR END HEADCOUNT ANALYSIS

2001 PLAN  
FINAL HEADCOUNT

	Book II AGU	Final (Oracle) AGU	Book I PLAN	Book II PLAN	Final (ORACLE) PLAN	Incr / (Decr) Final PLAN vs. Final AGU	Commentary
IM&T							
Net	298	292	264	264	257	(35)	
Gross	298	298	264	264	257	(41)	+36 Regular, -1 Temp, -70 SciPro
VENTURES							
Cardiovascular & Diabetes							
Net	0	0	0	0	0	0	
Gross	0	0	0	0	0	0	
Macrolide							
Net	41	41	46	46	42	1	+1 SciPro
Gross	41	41	46	46	42	1	
Anti-Viral							
Net	51	48	51	51	55	7	+7 Regular
Gross	55	55	55	55	57	2	
Anaesthesia							
Net	18	14	35	35	11	(3)	-2 Regular, -1 SciPro
Gross	18	16	35	35	11	(5)	
Urology							
Net	19	17	23	23	14	(3)	-1 Regular, -1 Contract, -1 SciPro
Gross	21	21	24	24	14	(7)	
Oncology / Transplant							
Net	35	36	38	38	47	11	+6 Regular, +1 Temp, +1 Contractor, +3 SciPro
Gross	42	42	43	43	47	5	
Total Ventures							
Net	184	158	183	183	169	13	
Gross	177	175	203	203	171	(4)	
DISCOVERY							
Net	778	778	778	778	770	(8)	-6 Regular, -6 Temp, +3 Contract, +1 SciPro
Gross	802	802	803	803	803	1	
DRUG SAFETY							
Net	200	195	206	206	189	(8)	-3 Regular, -3 Contractor
Gross	205	205	208	208	205	0	
PARD							
Net	344	330	344	344	337	7	+6 Regular, -2 Contractors
Gross	356	358	360	360	358	3	
PHASE I							
Net	57	56	76	76	62	6	+3 Regular, +3 Contractor
Gross	57	57	76	76	62	5	
DEV OPS							
Net	213	197	218	218	181	(15)	+2 Regular, -2 Temp, +6 Contract, -21 SciPro
Gross	213	213	220	220	186	(27)	
RA							
Net	57	64	69	69	68	4	+4 Regular
Gross	69	69	69	69	68	(1)	
MA							
Net	143	138	146	146	137	1	+4 Regular, -3 Contractor,
Gross	145	145	148	148	146	1	
ADMIN							
Net	88	82	85	85	113	31	+14 Regular, -1 Temp, +18 SciPro
Gross	88	82	85	85	113	31	
JUDGMENT							
Net	23	67	35	(4)	90	3	-26 Regular, +4 Temp, -1 Contract, +18 SciPro
Gross	35	41	51	7	73	32	
TOTAL							
Net	2,373	2,373	2,412	2,373	2,373	0	
Gross	2,443	2,443	2,487	2,443	2,443	0	

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01/20/01

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R&D PERSONNEL - 2001 PLAN													
DEC Actual	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	12-Mo Avg
<b>REGULAR</b>													
GROSS	1,968	2,180	2,170	2,175	2,167	2,162	2,146	2,145	2,153	2,181	2,178	2,174	2,194
UNFILL	...	(193)	(168)	(143)	(118)	(68)	(40)	(35)	(50)	(63)	(53)	(43)	(70)
NET	2,069	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124
<b>TEMPORARY</b>													
GROSS	13	21	21	21	21	34	56	56	50	22	22	22	22
UNFILL	...	...	...	...	...	...	...	...	...	...	...	...	...
NET	13	21	21	21	21	34	56	56	50	22	22	22	22
<b>CONTRACT</b>													
GROSS	87	80	78	79	76	78	76	77	73	74	73	75	75
UNFILL	...	...	...	...	...	...	...	...	...	...	...	...	...
NET	87	80	78	79	76	78	76	77	73	74	73	75	75
<b>SCIENTIFIC</b>													
GROSS	296	162	174	168	179	169	165	165	167	166	170	172	152
UNFILL	...	...	...	...	...	...	...	...	...	...	...	...	...
NET	296	162	174	168	179	169	165	165	167	166	170	172	152
<b>TOTAL EQUIV</b>													
GROSS	396	263	273	268	276	281	297	298	290	262	265	269	249
UNFILL	...	...	...	...	...	...	...	...	...	...	...	...	...
NET	396	263	273	268	276	281	297	298	290	262	265	269	249
<b>GRAND TOTAL</b>													
GROSS	2,364	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443
UNFILL	...	(193)	(168)	(143)	(118)	(68)	(40)	(35)	(50)	(63)	(53)	(43)	(70)
NET	2,364	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373
Div Contract	383	242	252	247	255	247	241	242	240	240	243	247	227

Monthly Changes												Total
J	F	M	A	M	J	J	A	S	O	N	D	
Regular	(82)	(15)	80	17	15	12	6	15			(7)	50
Temp						22	(6)	(23)				
Cont	(2)		(3)	2	(2)		(1)					(5)
Sci/Pro	(2)	(2)	(6)	(11)	(10)	(4)	(2)	(1)			(20)	(17)
Total	(82)	(25)	61	6	1	28	(5)	(13)	(10)	(10)	(27)	22

Quarterly Changes						
Beg	I	II	III	IV	End	
2001 PLAN	2,364	(64)	103	(23)	(7)	2,373
2000 ACTUALS	2,308	(78)	17	(15)	132	2,364
1999 ACTUALS	2,457	(311)	31	44	87	2,308
1998 ACTUALS	2,535	(90)	13	(71)	70	2,457
1997 ACTUALS	2,532	(239)	44	88	110	2,535

Total Adds	
Regular	26
Equivalent	170
Unfills	(70)

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Pharmaceutical Products Research & Development  
2001 Plan Headcount (Manmonth) Summary

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	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
<b>Information Management &amp; Technology</b>													
Regular	177	179	180	180	181	183	186	186	189	189	189	191	2,210
Temp/Summer	...	...	...	...	...	...	...	...	...	...	...	...	...
Contractors	...	...	...	...	...	...	...	...	...	...	...	...	...
Sci/Pro	78	79	74	72	72	72	71	71	70	69	67	66	861
Net Total	255	258	254	252	253	255	257	257	259	258	256	257	3,071
Unfills	...	...	...	...	...	...	...	...	...	...	...	...	...
Gross Total	255	258	254	252	253	255	257	257	259	258	256	257	3,071
<b>Ventures</b>													
Regular	138	140	140	143	146	147	147	147	147	147	147	147	1,736
Temp/Summer	3	3	3	3	3	3	3	3	3	3	3	3	36
Contractors	6	6	6	6	6	6	6	5	5	5	5	5	67
Sci/Pro	16	16	16	16	16	16	16	14	14	14	14	14	182
Net Total	163	165	165	168	171	172	172	169	169	169	169	169	2,021
Unfills	11	11	11	9	6	5	5	2	2	2	2	2	68
Gross Total	174	176	176	177	177	177	177	171	171	171	171	171	2,089
<b>Discovery</b>													
Regular	747	745	746	746	747	748	748	748	748	748	748	749	8,968
Temp/Summer	2	4	4	4	16	23	23	17	4	3	3	3	106
Contractors	20	20	20	19	19	19	18	17	17	17	17	17	220
Sci/Pro	1	1	1	1	1	1	1	1	1	1	1	1	12
Net Total	770	770	771	770	783	791	790	783	770	769	769	770	9,306
Unfills	33	33	32	33	32	31	31	33	33	34	34	33	392
Gross Total	803	803	803	803	815	822	821	816	803	803	803	803	9,698
<b>Drug Safety</b>													
Regular	179	180	184	184	184	184	184	184	184	184	184	184	2,199
Temp/Summer	...	...	...	...	...	13	13	13	...	...	...	...	39
Contractors	5	5	5	5	5	5	5	5	5	5	5	5	60
Sci/Pro	...	...	...	...	...	...	...	...	...	...	...	...	...
Net Total	184	185	189	189	189	202	202	202	189	189	189	189	2,298
Unfills	21	20	16	16	16	16	16	16	16	16	16	16	201
Gross Total	205	205	205	205	205	218	218	218	205	205	205	205	2,499
<b>Pharm Analytical R&amp;D</b>													
Regular	318	318	318	318	318	318	318	318	318	318	318	318	3,816
Temp/Summer	2	2	2	2	2	2	2	2	2	2	2	2	24
Contractors	17	17	17	17	17	17	17	17	17	17	17	17	204
Sci/Pro	...	...	...	...	...	...	...	...	...	...	...	...	...
Net Total	337	337	337	337	337	337	337	337	337	337	337	337	4,044
Unfills	22	22	22	22	22	22	22	22	22	22	22	22	264
Gross Total	359	359	359	359	359	359	359	359	359	359	359	359	4,308
<b>Phase-I Center</b>													
Regular	48	49	50	53	53	53	53	53	53	53	53	53	624
Temp/Summer	2	2	2	2	2	4	4	4	4	2	2	2	32
Contractors	8	8	7	7	7	7	7	7	7	7	7	7	86
Sci/Pro	...	...	...	...	...	...	...	...	...	...	...	...	...
Net Total	58	59	59	62	62	64	64	64	64	62	62	62	742
Unfills	1	3	3	...	...	...	...	...	...	...	...	...	7
Gross Total	59	62	62	62	62	64	64	64	64	62	62	62	749

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Pharmaceutical Products Research & Development  
2001 Plan Headcount (Manmonth) Summary

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	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
<b>Development Operations</b>													
Regular	148	148	148	148	148	150	150	150	150	150	150	150	1,790
Temp/Summer	1	1	1	1	1	1	1	1	1	1	1	1	12
Contractors	8	8	8	8	8	8	8	8	8	8	8	8	96
Sci/Pro	22	22	22	22	22	22	22	22	22	22	22	22	264
Net Total	179	179	179	179	179	181	181	181	181	181	181	181	2,162
Unfills	7	7	7	7	7	5	5	5	5	5	5	5	70
Gross Total	186	186	186	186	186	186	186	186	186	186	186	186	2,232
<b>Regulatory Affairs</b>													
Regular	57	58	60	62	62	62	62	62	62	62	62	62	733
Temp/Summer	1	1	1	1	1	1	1	1	1	1	1	1	12
Contractors	4	4	4	4	4	4	4	4	4	4	4	4	48
Sci/Pro	1	1	1	1	1	1	1	1	1	1	1	1	12
Net Total	63	64	66	68	68	68	68	68	68	68	68	68	805
Unfills	2	1	...	...	...	...	...	...	...	...	...	...	3
Gross Total	65	65	66	68	68	68	68	68	68	68	68	68	808
<b>Medical Affairs</b>													
Regular	112	115	119	122	122	124	125	125	125	125	125	125	1,464
Temp/Summer	1	1	3	3	3	5	5	5	1	1	1	1	30
Contractors	7	7	7	7	7	7	7	7	7	7	7	7	84
Sci/Pro	5	6	6	6	6	5	4	4	4	4	4	4	58
Net Total	125	129	135	138	138	141	141	141	137	137	137	137	1,636
Unfills	17	13	10	9	9	9	9	9	9	9	9	9	121
Gross Total	142	142	145	147	147	150	150	150	146	146	146	146	1,757
<b>Administration</b>													
Regular	88	88	88	88	88	88	88	88	88	88	88	88	1,056
Temp/Summer	2	2	2	2	2	2	2	2	2	2	2	2	24
Contractors	5	3	5	3	5	3	5	3	4	3	5	5	49
Sci/Pro	18	18	18	18	18	18	18	18	18	18	18	18	216
Net Total	113	111	113	111	113	111	113	111	112	111	113	113	1,345
Unfills	...	...	...	...	...	...	...	...	...	...	...	...	...
Gross Total	113	111	113	111	113	111	113	111	112	111	113	113	1,345
<b>Judgment</b>													
Regular	(25)	(18)	(1)	5	45	49	49	42	54	61	67	57	385
Temp/Summer	7	5	3	3	4	2	2	2	4	7	7	7	53
Contractors	...	...	...	...	...	...	...	...	...	...	...	...	...
Sci/Pro	21	31	30	43	33	30	32	36	36	41	45	26	404
Net Total	3	18	32	51	82	81	83	80	94	109	119	90	842
Unfills	79	58	42	22	(24)	(48)	(53)	(37)	(24)	(35)	(45)	(17)	(82)
Gross Total	82	76	74	73	58	33	30	43	70	74	74	73	924
<b>Total Plan Detail</b>													
Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temp/Summer	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors	80	78	79	76	78	76	77	73	74	73	75	75	914
Sci/Pro	162	174	168	179	169	165	165	167	166	170	172	152	2,009
Net Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Gross Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316

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Pharmaceutical Products Research & Development  
2001 Plan Headcount (Manmonth) Summary

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	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total Man Months
<b>From Heads Tab</b>													
Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temporary/Summ	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors	85	83	85	85	85	84	86	84	85	84	85	85	1,016
Sci/Pro	157	169	162	170	162	157	156	156	155	159	162	142	1,907
Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316
<b>Detail &gt; Corp Submission</b>													
Regular	...	...	...	...	...	...	...	...	...	...	...	...	...
Temporary/Summ	...	...	...	...	...	...	...	...	...	...	...	...	...
Contractors/Sci Pr	...	...	...	...	...	...	...	...	...	...	...	...	...
Total	...	...	...	...	...	...	...	...	...	...	...	...	...
Unfills	...	...	...	...	...	...	...	...	...	...	...	...	...
Total	...	...	...	...	...	...	...	...	...	...	...	...	...
<b>2001 Corp Submission</b>													
Regular	1,987	2,002	2,032	2,049	2,094	2,106	2,110	2,103	2,118	2,125	2,131	2,124	24,981
Temporary/Summ	21	21	21	21	34	56	56	50	22	22	22	22	368
Contractors/Sci Pr	242	252	247	255	247	241	242	240	240	243	247	227	2,923
Total	2,250	2,275	2,300	2,325	2,375	2,403	2,408	2,393	2,380	2,390	2,400	2,373	28,272
Unfills	193	168	143	118	68	40	35	50	63	53	43	70	1,044
Total	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	2,443	29,316

## Oracle Report 01/31/01

Regular	2,012	2,020	2,033	2,051	2,049	2,057	2,069	2,061	2,061	2,064	2,064	2,067	24,608
Temporary/Summ	14	16	18	18	30	54	54	54	48	18	15	15	354
Contractors	80	78	79	76	78	76	77	77	73	74	75	75	918
Sci/Pro	141	143	138	135	136	135	133	133	131	130	127	126	1,608
Total	2,247	2,257	2,268	2,280	2,293	2,322	2,333	2,325	2,313	2,286	2,281	2,283	27,488
Unfills	114	110	101	89	92	88	79	88	87	87	88	87	1,110
Total	2,361	2,367	2,369	2,369	2,385	2,410	2,412	2,413	2,400	2,373	2,369	2,370	28,598

## Check figure Oracle vs details before judgement

Regular	...	...	...	7	...	...	8	...	(3)	...	...	...	12
Temporary/Summ	...	...	...	...	...	...	...	6	30	3	...	...	39
Contractors	...	...	...	...	...	...	...	4	(1)	1	...	...	4
Sci/Pro	...	...	...	(1)	...	...	...	2	1	1	...	...	3
Total	...	...	...	6	...	...	8	12	27	5	...	...	58
Unfills	...	...	...	(7)	...	...	(9)	1	...	(1)	...	...	(16)
Total	...	...	...	(1)	...	...	(1)	13	27	4	...	...	42

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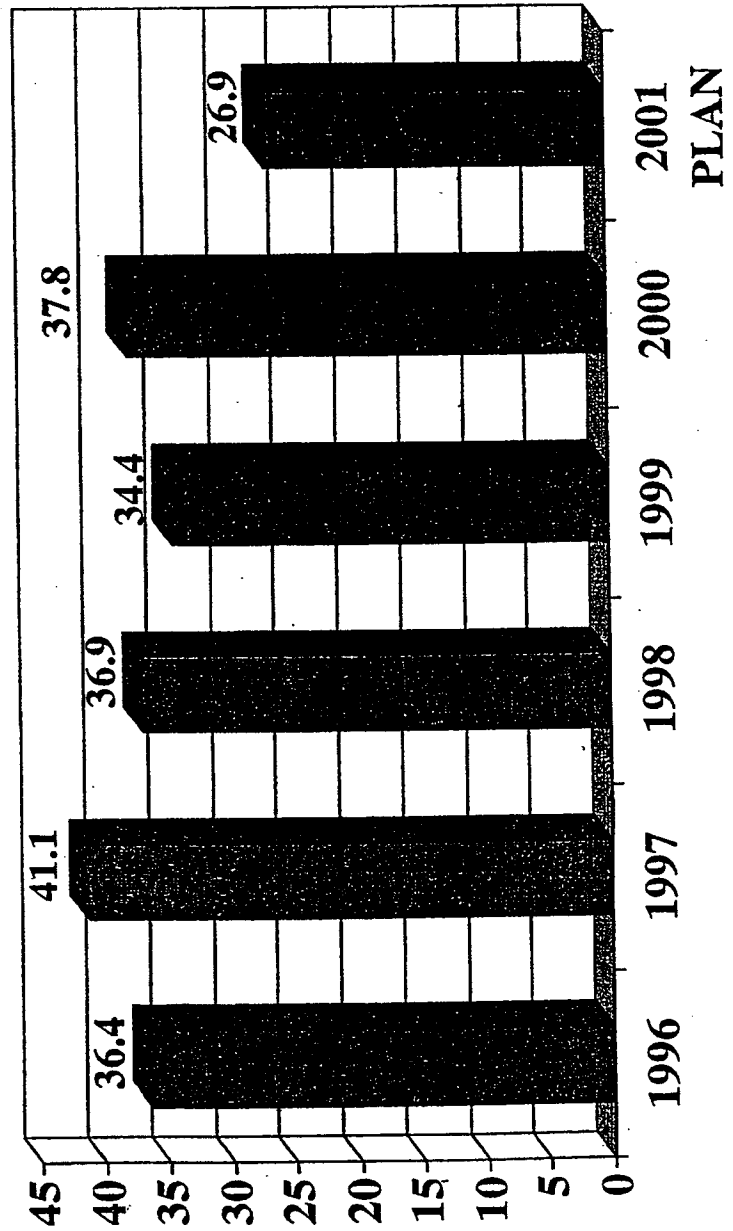


***Capital***

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# R&D Capital 1996-2001 (\$MM's)

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**2001 PLAN Capital  
Pharmaceutical Products Research & Development**

*Final Plan*

	2000 AGU	2001 PLAN	\$ Fav/(Unfav)	% Fav/(Unfav)
<b>Authorizations</b>				
IM&T	6,672	4,748	1,924	28.8%
Discovery	11,268	7,626	3,642	32.3%
Drug Safety	3,520	3,125	395	11.2%
PARD	3,485	5,805	(2,320)	-66.6%
Admin	12,390	3,480	8,910	71.9%
Dev Ops	100	100	0	0.0%
Medical Affairs	50	50	0	0.0%
RA/QA	10	10	0	0.0%
Other	283	2,000	(1,717)	-806.7%
<b>Total</b>	<b>37,778</b>	<b>26,944</b>	<b>10,834</b>	<b>28.7%</b>

**Project Expense**

IM&T	8,631	2,090	6,541	75.8%
Discovery	1,095	892	203	18.5%
Drug Safety	272	17	255	93.8%
PARD	425	828	(403)	-94.8%
Admin	1,499	743	756	50.4%
Dev Ops	9	9	0	0.0%
Medical Affairs	11	11	0	0.0%
RA/QA	4	4	0	0.0%
Other	4	0	4	100.0%
Judgment	(1,722)	400	(2,122)	123.2%
<b>Total</b>	<b>10,228</b>	<b>4,994</b>	<b>5,234</b>	<b>51.2%</b>

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Pharmaceutical Products Research & Development  
2001 PLAN Capital[illegible]

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**PHARMACEUTICAL PRODUCTS DIVISION  
RESEARCH & DEVELOPMENT  
PROPOSED CAPITAL PROJECTS <\$250M**

	2000 AGU	2001 Authorizations	01 Funded v. '00 AGU
		Requests      Funded      Unfunded	
IM&T *	3,196	3,787      2,538      1,249	658
Development Ops	100	100      100      0	0
Discovery	4,670	4,027      4,027      0	643
Drug Safety	2,050	2,809      2,050      759	0
PARD	2,455	3,092      2,455      637	0
Medical Affairs	50	45      50      (5)	0
RA/QA	10	20      10      10	0
Other	283	0      2,000      (2,000)	(1,717)
<b>Total</b>	<b>12,814</b>	<b>13,880      13,230      650</b>	<b>(416)</b>

\* Includes \$1,545M for PC refresh and new employees.

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**2001 Plan Task Exercise  
Pharmaceutical Products Division  
Research and Development  
(\$MM)**

**Capital Projects**

Project Name	Capital Auth	Project Exp	Commentary
<b>Admin:</b>			
- Delay AEGIS Wave III to 2002	2,000	-	
- Reduce lab renovations	2,000	440	
Subtotal Admin	4,000	440	-Pharmacology Labs & AP9/G19 Renovations
<b>IM&amp;T:</b>			
- Reduce PC Refresh / Asset Mgmt	400	-	Assume 4 year refresh vs. 3 year
- NT Storage Mgmt	554	154	Pending IM&T's approval. There is \$577 of functional expense associated with this project.
- Under \$250 project expense reduced	-	442	
Subtotal IM&T	1,054	596	
<b>Discovery:</b>			
- Therapeutic Area Projects Support	168	1,882	Listed as an IM&T project in capital file. There is \$544 of functional expense associated with this project.
- HTS Expansion	1,030	300	Pending D. Norbeck's approval
- Genomics Expansion	550	480	Pending D. Norbeck's approval
- Bring under \$250 back to original request amount	643	-	Pending D. Norbeck's approval
- Under \$250 project expense reduced	-	200	Pending D. Norbeck's approval
Subtotal Discovery	2,401	2,822	
<b>Drug Safety:</b>			
- LC/MS	1,910	120	
- Lab Renovation AP13A	-	-	
- Gene Expression	411	1,044	
- Under \$250 project expense reduced	-	-	
Subtotal Drug Safety	2,321	1,164	
<b>PARD:</b>			
- Potent Drug Encapsulator	500	100	
- Under \$250 project expense reduced	-	400	
Subtotal PARD	500	500	
<b>Other:</b>			
- Eliminate Judgment	283	478	
- Unidentified Reverse Task	(2,000)	(400)	
<b>Total Impact</b>	<b>6,559</b>	<b>5,600</b>	

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	Capital Authorizations		Proj Expense	
	> 250	< 250	> 250	< 250
IM&T	2,210	2,538	1,112	978
Discovery	3,599	4,027	537	355
Drug Safety	1,075	2,050	5	12
PARD	3,350	2,455	640	188
Admin	3,480	-	743	-
Dev Ops	-	100	-	9
Med Affairs	-	50	-	11
RA/QA	-	10	-	4
Other	-	2,000	-	400
<b>Total</b>	<b>13,714</b>	<b>13,230</b>	<b>3,037</b>	<b>1,957</b>
				<b>4,994</b>

# PART 3

# ***Balance Sheet***

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Balance Sheet Galling Sur note this is exactly as it appears in the J:\Drive

PHARMACEUTICAL PRODUCTS DIVISION  
DETAIL OF ACCOUNTS PAYABLE, ACCRUED EXPENSES

CATEGORY	Actual 12/31/97	Actual 12/31/98	Actual 12/31/99	AGU 12/31/00	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	13 MO AVG
SALARIES, WAGES & COMMISSIONS Mgmt Incentive plans - R&D	(2,960)	(2,636)	(3,021)	(3,022)	(3,272)	(3,524)	(754)	(1,009)	(1,259)	(1,510)	(1,762)	(2,014)	(2,266)	(2,518)	(2,770)	(3,022)	(2,440)
OTHER ACCRUED LIABILITIES Clinical Grants - R&D	(75,827)	(57,768)	(38,947)	(54,786)	(59,150)	(62,256)	(64,128)	(62,637)	(61,651)	(61,501)	(63,815)	(49,468)	(46,131)	(43,825)	(44,717)	(43,761)	(53,284)
Drug Safety Grant Accrual - R&D	(499)	(666)	(673)	(584)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(596)	(591)
Misc R&D	(9,921)	(5,511)	(8,742)	(9,007)	(11,102)	(10,037)	(10,390)	(9,351)	(11,027)	(10,063)	(11,320)	(12,764)	(10,161)	(13,071)	(11,521)	(7,575)	(10,266)
OTHER ACCRUED LIABILITIES	(86,247)	(63,845)	(46,362)	(64,357)	(89,859)	(72,879)	(75,104)	(72,774)	(73,264)	(72,150)	(65,721)	(62,616)	(56,878)	(57,482)	(56,824)	(51,922)	(64,189)
TOTAL AP & ACCRUED EXP.	(89,207)	(66,481)	(49,383)	(87,379)	(73,110)	(78,403)	(75,868)	(73,779)	(74,923)	(73,649)	(67,483)	(64,932)	(59,144)	(60,000)	(59,594)	(54,944)	(69,609)

PHARMACEUTICAL PRODUCTS DIVISION  
DETAIL OF PREPAID EXP. AND OTHER RECEIVABLES

CATEGORY	Actual 12/31/97	Actual 12/31/98	Actual 12/31/99	AGU 12/31/00	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	13 MO AVG
PREPAID EXPENSE Spare/change parts (R&D)	464	414	438	422	432	432	432	432	432	432	432	432	432	432	432	432	432
Ligand Contract	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tigabine Reserve	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clinical R & D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL PREPAID EXPENSE	464	414	438	422	432	432	432	432	432	432	432	432	432	432	432	432	432
OTHER RECEIVABLES Travel advance (R&D)	573	305	170	325	576	576	576	576	576	576	576	576	576	576	576	288	509
TOTAL PREPAID AND OTHER RECEIVABLE	1,037	719	608	747	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	1,008	720	941

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INITIAL GRANT BALANCE SHEET GAITING  
 PRD 348-300  
 101 PLAN

	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Beginning G/L Balance	(53,000)	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(49,468)	(46,131)	(43,825)	(44,717)	
Payments	8,945	8,867	11,077	11,796	11,421	10,547	12,283	9,231	9,461	9,393	8,781	10,754	122,556
Adjusted Grants (per P&L gaiting)	(14,095)	(12,973)	(12,948)	(10,506)	(10,235)	(10,397)	(4,597)	(4,864)	(6,124)	(7,087)	(9,673)	(9,798)	(113,317)
Grant Gaiting Adjustments													...
Adjusted Grants	(14,085)	(12,973)	(12,948)	(10,506)	(10,235)	(10,397)	(4,597)	(4,864)	(6,124)	(7,087)	(9,673)	(9,798)	(113,317)
Other	...	...	...	...	...	...	...	...	...	...	...	...	...
Ending G/L Balance	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(49,468)	(46,131)	(43,825)	(44,717)	(43,761)	
Indpostings :													
Debit Balances	...	...	...	...	...	...	...	...	...	...	...	...	...
Other	...	...	...	...	...	...	...	...	...	...	...	...	...
Ending MFRP Balance	(58,150)	(62,256)	(64,128)	(62,837)	(61,651)	(61,501)	(53,815)	(49,468)	(46,131)	(43,825)	(44,717)	(43,761)	
29-Sep-00 02:07 PM													
GROUP/PLANNING/2001 PLAN/Balance Sheet(Bal_sht.xls)/grants													
96 Actual Pay as % of BB	22.25%	19.15%	30.89%	15.59%	20.20%	10.84%	25.05%	19.13%	20.28%	13.89%	21.79%	22.13%	
97 Actual Pay as % of BB	12.28%	6.62%	10.12%	14.98%	22.46%	11.48%	11.21%	12.60%	7.44%	9.08%	8.81%	14.55%	
98 Actual Pay as % of BB	3.62%	7.21%	5.93%	7.71%	9.64%	10.15%	9.46%	5.78%	8.98%	11.16%	8.68%	16.24%	
99 Actual Pay as % of BB	10.49%	10.81%	8.16%	19.70%	4.49%	19.73%	17.90%	12.52%	19.59%	25.64%	18.05%	20.91%	
Our year average	12.16%	10.95%	13.78%	14.50%	14.20%	13.05%	15.91%	12.51%	14.07%	14.94%	14.33%	18.46%	
96 Actual	18,915	25,781	25,749	26,740	25,881	31,230	29,251	27,202	25,939	25,579	24,839	24,988	
97 Actual	40,699	46,087	49,433	48,752	44,188	47,590	50,515	55,955	62,751	64,406	67,079	75,827	
98 Actual	78,671	78,485	79,324	78,977	75,397	70,808	69,331	66,581	65,681	66,716	62,790	60,600	
99 Actual	57,702	57,392	58,501	51,012	49,767	47,310	39,852	33,259	34,582	36,331	40,172	43,640	
Our year average	48,897	51,936	53,252	51,370	48,808	49,235	47,237	45,749	47,238	48,258	48,720	51,264	

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# *Depreciation*

**Pharmaceutical Products Division R&D**  
**2001 Depreciation Estimate vs. 2000 Depreciation**  
**By Division**

Division	2001 Est. Base Depr*	2001 Estimated Depr. of Projects from 5/00-12/00	2001 Estimated Depr. for '01 Transfer	Judgement	2001 Est. Total Depr.	2000 Depreciation	\$ Inc/(Dec)	% Inc/(Dec)
42-IM&T	4,385	1,056	285	(134)	5,592	6,253	(661)	-10.6%
43-Ventures	293	24	8	(5)	319	276	43	15.6%
44-Discovery	11,103	1,756	689	(383)	13,165	12,906	259	2.0%
46-Drug Safety	2,703	23	482	(258)	2,950	3,046	(96)	-3.2%
47-PARD	3,721	235	270	(206)	4,020	4,428	(408)	-9.2%
49-Phase I Center	244	2	9	(7)	248	205	43	21.0%
52-Development Ops.	1,535	1	10	(8)	1,538	1,405	133	9.5%
53-RA/QA	90	8	4	(4)	98	68	30	44.1%
54-Medical Affairs	208	9	8	(6)	220	182	38	20.9%
55-Admin	448	2,699	43	(33)	3,157	2,031	1,126	55.4%
	<u>24,730</u>	<u>5,813</u>	<u>1,808</u>	<u>(1,043)</u>	<u>31,307</u>	<u>30,800</u>	<u>507</u>	<u>1.7%</u>

\* Based on the FAR 50 Report dated 5/00.

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**Floorspace**

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**PPD R&D  
FLOOR SPACE SUMMARY  
2001 PLAN**

Items	2000	1st Pass 2001	2nd Pass 2001	1st Pass		2nd Pass	
				VARIANCE INCR/(DECR)	%	VARIANCE INCR/(DECR)	%
CED	36,807,916	38,691,048	38,777,826 <sup>1</sup>	1,883,132	5.1%	1,969,910	5.4%
J23/J25- Amhurst	457,449	480,322	464,991 <sup>2</sup>	22,672	5.0%	7,542	1.6%
J35 -Carriage pt	351,680	369,264	343,466 <sup>4</sup>	17,584	5.0%	(8,214)	(2.3%)
J28/MIS	408,769	429,207	406,341 <sup>3</sup>	20,438	5.0%	(2,428)	(0.6%)
Unidentified Space	40,058	42,061	41,860	2,003	n/a	1,802	n/a
Plug (s/b zero)	0	0	0	0	0.0%	0	0.0%
<b>Total</b>	<b>38,065,872</b>	<b>40,031,902</b>	<b>40,034,484</b>	<b>1,946,030</b>	<b>5.1%</b>	<b>1,968,112</b>	<b>5.2%</b>

<sup>1</sup> Input per CED Report Pass #1 dated 6/29/00 and CED Report Pass #2 dated 9/1/00 plus the adjustment for D-472. This adjustment was detailed in John Urth's memo dated 1/29/2001. The adjustment equals \$21,424 for additional space in D-472 as requested by J. Hammerlin.

<sup>2</sup> Per CED Report (dated 9/1/00) and Division Summary from P. Kadish (dated 9/28/00).

Note: Amhurst rates for 2001 PLAN went up by 1.65% versus 2000 PLAN. (Sq. ft. are obtained from CED memo, while \$\$'s are obtained from Division memo.

<sup>3</sup> Per memo received from Sarah Schaefer on 8/21/00 per S. Schaefer 10/1/99.

<sup>4</sup> Carriage Point charges to be allocated, calculated as follows:

Lease charge from Legal (R. Potoczek) of \$479,832 for 2001  
Total expenses of \$716,633 allocated between Marketing and R&D based on square feet occupied.

Total lease charges	\$479,832	31,400
Less Stackcard to T. Thompson	(\$136,368)	(5,975)
Net charge to Discovery	<u>\$343,466</u>	<u>25,425</u>

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PPD R&D  
DIVISIONAL VARIANCE SUMMARY  
2001 PLAN  
FLOORSPACE

Division	Total Dollars (\$000's)			Total Square Feet			Average Rate					
	2000	2001	Inc/(Dec)	% Inc/(Dec)	2000	2001	Inc/(Dec)	% Inc/(Dec)	2000	2001	Inc/(Dec)	% Inc/(Dec)
IM&T	1,884.4	1,928.9	44.5	2.4%	50,847	50,792	(55)	(0.1%)	\$37.06	\$37.98	\$0.92	2.5%
Ventures	1,051.3	1,015.4	(34.8)	(3.3%)	28,928	28,878	(50)	(0.2%)	\$36.34	\$36.10	-\$0.24	(0.7%)
Discovery	18,526.8	19,520.7	993.9	5.4%	394,962	395,515	553	0.2%	\$50.76	\$53.41	\$2.64	5.2%
Drug Safety	7,582.9	7,908.3	325.4	4.3%	146,938	144,747	(2,191)	(1.5%)	\$51.96	\$54.64	\$2.68	5.2%
PARC	5,855.2	6,154.6	299.4	5.1%	144,895	144,586	(309)	(0.2%)	\$40.42	\$42.57	\$2.15	5.3%
Phase I Center	286.9	301.2	14.4	5.0%	4,690	4,690	0	0.0%	\$61.17	\$64.23	\$3.06	5.0%
Development Ops	1,441.1	1,357.7	(83.5)	(5.8%)	38,734	33,938	(4,796)	(12.4%)	\$37.21	\$40.00	\$2.80	7.5%
Regulatory Affairs	434.6	464.4	29.7	6.8%	12,135	12,375	240	2.0%	\$35.82	\$37.52	\$1.71	4.8%
Medical Affairs	559.6	676.6	119.0	21.3%	17,204	19,058	1,852	10.8%	\$32.52	\$35.61	\$3.08	9.5%
Administration	443.1	702.7	259.6	58.6%	10,164	15,556	5,492	54.0%	\$43.59	\$44.88	\$1.29	3.0%
<b>Total</b>	<b>35,117.3</b>	<b>34,351.5</b>	<b>(765.8)</b>	<b>(2.2%)</b>	<b>1,160,172</b>	<b>1,160,172</b>	<b>0</b>	<b>0.0%</b>	<b>\$30.26</b>	<b>\$29.52</b>	<b>-\$0.74</b>	<b>(2.4%)</b>
<b>Less Carriage Point</b>	<b>(351.7)</b>	<b>(343.5)</b>	<b>8.2</b>	<b>(2.3%)</b>	<b>...</b>	<b>...</b>	<b>...</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>
<b>Total</b>	<b>34,765.6</b>	<b>34,008.0</b>	<b>(757.6)</b>	<b>(2.2%)</b>	<b>1,160,172</b>	<b>1,160,172</b>	<b>0</b>	<b>0.0%</b>	<b>\$30.26</b>	<b>\$29.52</b>	<b>-\$0.74</b>	<b>(2.4%)</b>

(a) Primarily due to Clinical Pharmacokinetic (D-4PK) receiving 1,107 sq. ft. in AP9 for 2001 PLAN.

(b) Primarily due to Statistics (D-436) re-allocating their space to Outcomes research (D-42); Med. Affairs and Decision Analysis (D-4NP; Admin.).

(c) Primarily due to R&D Ops (D-477) receiving and additional 644 sq. ft. in AP6A and due to Outcomes Research (discussed in footnote (b) above).

LOCATIONS: 1/1/2001 PLAN: PPD R&D Divisional Variance Summary

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**PPD R&D  
BUILDING VARIANCE SUMMARY  
2001 PLAN  
FLOORS/SPACE**

Building	Total Dollars (\$000's)			Total Square Feet			Average Rate		
	2000	2001	% Inc/(Dec)	2000	2001	% Inc/(Dec)	2000	2001	% Inc/(Dec)
A1	11.9	12.6	0.7	384	384	0	\$31.02	\$32.88	6.0%
A4	231.1	242.2	4.8%	6,358	6,358	0	\$36.34	\$38.10	4.9%
AP10	4,803.3	5,124.0	6.7%	101,288	101,284	(4)	\$48.41	\$50.59	4.5%
AP13	1,740.0	1,812.8	4.2%	35,503	35,503	(108)	\$48.86	\$51.06	4.5%
AP13A	4,498.7	4,722.8	5.0%	73,529	73,529	(31)	\$61.17	\$64.23	5.0%
AP16	151.0	165.4	9.5%	11,931	12,273	342	\$12.66	\$13.48	6.5%
AP16A	134.0	131.1	(2.2%)	5,080	4,418	(642)	\$26.49	\$29.67	12.0%
AP20	163.5	172.5	5.5%	3,861	3,861	0	\$42.35	\$44.68	5.5%
AP3	883.2	929.5	5.2%	25,885	25,885	0	\$34.12	\$35.91	5.2%
AP30	930.2	975.2	4.8%	25,598	25,598	0	\$36.10	\$37.16	2.8%
AP31	851.5	907.9	6.6%	14,784	14,784	0	\$58.35	\$61.49	5.4%
AP34	237.7	256.4	7.7%	6,782	6,782	240	\$38.34	\$38.10	0.6%
AP52	5,095.9	5,375.8	5.5%	85,753	85,753	0	\$59.42	\$62.69	5.5%
AP6A	506.0	528.3	4.4%	13,866	13,866	(69)	\$36.34	\$38.10	4.8%
AP6B	832.1	872.4	4.8%	22,897	22,897	0	\$36.34	\$38.10	4.8%
AP6C	53.6	0.0	(100.0%)	1,476	0	(1,476)	\$36.34	\$0.00	(100.0%)
AP6D	25.3	32.3	27.4%	697	847	150	\$38.10	\$38.10	0.0%
AP9	3,606.8	3,823.1	6.0%	83,202	83,202	0	\$43.35	\$45.95	6.0%
AP8A	4,368.3	4,627.3	5.9%	100,767	100,690	(77)	\$43.35	\$45.95	6.0%
AP8B	466.1	494.1	6.0%	10,752	10,752	0	\$43.35	\$45.95	6.0%
J2	40.3	42.7	5.9%	2,789	2,789	0	\$14.45	\$15.32	6.0%
J23 (Amhurst)	185.1	188.2	1.7%	7,323	7,323	0	\$25.70	\$26.70	3.9%
J25 (Amhurst)	272.3	276.8	1.6%	10,777	10,777	0	\$25.27	\$25.69	1.6%
J28 (North Point--MIS)	408.8	406.3	(0.6%)	12,262	12,262	0	\$33.34	\$33.14	(0.6%)
J35 (Carriage Point)	351.7	343.5	(2.3%)	1,168	1,168	0	N/A	N/A	N/A
M2	28.6	30.5	6.7%	1,168	1,168	0	\$24.48	\$26.13	6.7%
M3	611.3	637.2	4.2%	32,742	31,970	(772)	\$18.67	\$19.83	6.2%
R1	166.9	161.0	(3.5%)	5,035	4,571	(364)	\$33.14	\$34.47	4.0%
R12	353.9	369.8	4.5%	5,731	5,731	0	\$61.76	\$64.54	4.5%
R13	2,854.6	2,983.0	4.5%	45,571	45,571	0	\$62.64	\$65.46	4.5%
R14	878.8	937.3	6.7%	12,596	12,596	(41)	\$69.54	\$74.41	7.0%
R18	1,041.3	1,219.8	17.1%	28,807	28,807	2,147	\$36.06	\$42.34	8.4%
R2	331.4	357.4	7.8%	9,549	9,549	259	\$34.70	\$36.44	5.0%
R8	839.8	873.5	4.0%	15,914	15,916	2	\$52.77	\$54.88	4.0%
<b>TOTAL</b>	<b>48,068.1</b>	<b>50,634.1</b>	<b>5.3%</b>	<b>1,145,167</b>	<b>1,145,167</b>	<b>(1,476)</b>	<b>\$43.34</b>	<b>\$45.95</b>	<b>6.0%</b>
<b>Less Carriage Point</b>	<b>(351.7)</b>	<b>(343.5)</b>	<b>2.3%</b>	<b>...</b>	<b>...</b>	<b>...</b>	<b>N/A</b>	<b>N/A</b>	<b>N/A</b>
<b>TOTAL</b>	<b>47,716.4</b>	<b>50,290.6</b>	<b>5.3%</b>	<b>1,145,167</b>	<b>1,145,167</b>	<b>(1,476)</b>	<b>\$43.34</b>	<b>\$45.95</b>	<b>6.0%</b>

- (a) Primarily due to PARD's Intermediate Scale Up facilities (D-4P9) accounting for 488 sq. ft. and \$6.6 over year 2000.  
 (b) Primarily due to PARD's Intermediate Scale Up facilities (D-4P9) using less space in AP16A and more in AP16.  
 (c) Due to Outcomes Research (D-42J) no longer needing space in AP6C.  
 (d) Primarily due to an incorrect allocation on the Floor plans (D-431). Amount will reside in D-A54 until Floor plan can be updated.  
 (e) Per Carriage Point lease, Discovery is occupying 25,425 sq. ft. in J35.  
 (f) Includes charge of \$41.9 for R13 Unidentified space (per Division allocation).  
 (g) Primarily due to PARD's Dislocation (D-4P4) occupying more space; partially offset by PARD Process Support (D-4P8) needing less space.  
 (h) Due to PARD's Pharm. Analysis & Stability occupying more space.

<b>MEMO:</b>	
CED Rate	Increased by 5.3%
Amhurst Rate	Increased by 1.6%
North Point Charges	Decreased by 0.6%
Carriage Point Charges	Decreased by 2.3% due to commercial assuming responsibility for 600 sq. ft. more over year 2000.

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# ***Misc. Fixed Expenses (Burden File)***

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**PPD**  
**Overhead Costs - Absorbed**  
**GROSS (\$000)**

	2000 AGU	2001 Plan	2001 APU	2001 AGU	01 Plan II(D) vs. 00 AGU \$	%	Source
1 <b>PPD Admin Exp Assignments 790-850-A54 (via PPD Div FP&amp;A)</b>	485.0			485.0	485.0	8.7%	Corp Admin Exp Assignments 790-850-A54 (via PPD Div FP&A)
2 <b>Other Cost Expense Pools 790-851-A54 (via PPD Div FP&amp;A)</b>	450.4			450.4	450.4	9.0%	Other Cost Expense Pools 790-851-A54 (via PPD Div FP&A)
3 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b> (When transferring to OpCost, take this total less Satellite Copier charges)	835.4			835.4	835.4	8.9%	Other Cost Expense Pools (via PPD Div FP&A)
4 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b> (When transferring to OpCost, take this total less Satellite Copier charges)	-120.7			-120.7	-120.7	-5.609.3	Other Cost Expense Pools (via PPD Div FP&A)
5 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	0.0			0.0	0.0	-0.5%	Other Cost Expense Pools (via PPD Div FP&A)
6 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-1.0			-1.0	-1.0	-0.5%	Other Cost Expense Pools (via PPD Div FP&A)
7 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	587.0			587.0	587.0	39.8%	Other Cost Expense Pools (via PPD Div FP&A)
8 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-0.1			-0.1	-0.1	-0.1%	Other Cost Expense Pools (via PPD Div FP&A)
9 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	84.4			84.4	84.4	19.2%	Other Cost Expense Pools (via PPD Div FP&A)
10 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-1.9			-1.9	-1.9	-2.2%	Other Cost Expense Pools (via PPD Div FP&A)
11 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-48.2			-48.2	-48.2	-19.7%	Other Cost Expense Pools (via PPD Div FP&A)
12 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	107.0			107.0	107.0	39.9%	Other Cost Expense Pools (via PPD Div FP&A)
13 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	710.3			710.3	710.3	28.2%	Other Cost Expense Pools (via PPD Div FP&A)
14 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-48.0			-48.0	-48.0	-5.1%	Other Cost Expense Pools (via PPD Div FP&A)
15 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	5.7			5.7	5.7	4.0%	Other Cost Expense Pools (via PPD Div FP&A)
16 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	50.0			50.0	50.0	7.2%	Other Cost Expense Pools (via PPD Div FP&A)
17 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	14.0			14.0	14.0	12.1%	Other Cost Expense Pools (via PPD Div FP&A)
18 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	17.0			17.0	17.0	0.4%	Other Cost Expense Pools (via PPD Div FP&A)
19 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-324.0			-324.0	-324.0	-100.0%	Other Cost Expense Pools (via PPD Div FP&A)
20 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-307.0			-307.0	-307.0	-6.1%	Other Cost Expense Pools (via PPD Div FP&A)
21 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	11.0			11.0	11.0	2.7%	Other Cost Expense Pools (via PPD Div FP&A)
22 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	0.0			0.0	0.0	0.0%	Other Cost Expense Pools (via PPD Div FP&A)
23 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	0.0			0.0	0.0	0.0%	Other Cost Expense Pools (via PPD Div FP&A)
24 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	71.2			71.2	71.2	16.1%	Other Cost Expense Pools (via PPD Div FP&A)
25 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-1.0			-1.0	-1.0	-0.7%	Other Cost Expense Pools (via PPD Div FP&A)
26 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	74.8			74.8	74.8	4.0%	Other Cost Expense Pools (via PPD Div FP&A)
27 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	144.8			144.8	144.8	5.9%	Other Cost Expense Pools (via PPD Div FP&A)
28 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	3.0			3.0	3.0	5.0%	Other Cost Expense Pools (via PPD Div FP&A)
29 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	504.0			504.0	504.0	35.0%	Other Cost Expense Pools (via PPD Div FP&A)
30 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	39.0			39.0	39.0	100.0%	Other Cost Expense Pools (via PPD Div FP&A)
31 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	5.2			5.2	5.2	4.0%	Other Cost Expense Pools (via PPD Div FP&A)
32 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-4,109.0			-4,109.0	-4,109.0	-37.0%	Other Cost Expense Pools (via PPD Div FP&A)
33 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	0.0			0.0	0.0	0.0%	Other Cost Expense Pools (via PPD Div FP&A)
34 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-4,109.0			-4,109.0	-4,109.0	-38.7%	Other Cost Expense Pools (via PPD Div FP&A)
35 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	-2,163.4			-2,163.4	-2,163.4	-5.1%	Other Cost Expense Pools (via PPD Div FP&A)
36 <b>Other Cost Expense Pools (via PPD Div FP&amp;A)</b>	0.0			0.0	0.0	0.0%	Other Cost Expense Pools (via PPD Div FP&A)

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**PPD R&D**  
**2001 Fixed Allocations/Charges**  
**GROSS (\$000)**

Direct to Departments (Stack Card)	2000	2001	2001	2001	01 Plan I/(D) vs. '00 AGU		Notes
	AGU	Plan	APU	AGU	\$	%	
PPNC Allocations							
11 Wisdom to Product Development and RA/Q	328.7	322.7	322.7	322.7	-6.0	-1.8%	PPD Ops Fixed (T. Dee / J. Truax)
12 Other to Product Development	2,031.0	3,044.6	3,044.6	3,044.6	1,013.6	49.9%	PPD Ops Fixed (T. Dee / J. Truax)
13 Housekeeping	187.1	187.1	187.1	187.1	0.0	0.0%	Pulls from Misc. Fixed Tab
14 Whse. Handling Fixed Allocation	0.0	86.5	86.5	86.5	86.5	#DIV/0!	Pulls from Misc. Fixed Tab
Other							
15 Amortization Svc Loaners	26.5	26.5	26.5	26.5	0.0	0.0%	Pulls from Misc. Fixed Tab
16 Utilities	99.6	99.5	99.5	99.5	-0.1	-0.1%	Pulls from Misc. Fixed Tab
17 Corp Copier Fixed Costs	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
18 R&D Internal Allocation	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
19 ABC Allocations	0.0	0.0	0.0	0.0	0.0	0.0%	Pulls from Misc. Fixed Tab
Subtotal PPNC/Other	2,672.9	3,766.9	3,766.9	3,766.9	1,094.0	40.9%	
Corporate Reallocations							
3 Subtotal Other Cost Expense Pools	n/a	n/a	n/a	n/a	#VALUE!		N/A
R&D Allocations							
Input Depreciation	32,662.6	31,308.5	31,308.5	31,308.5	-1,354.1	-4.1%	L:\GROUP\PLANNING\2001 PLAN\Floorspace\01floor.xls
Input Floor Space	37,329.0	40,013.1	40,013.1	40,013.1	2,684.1	7.2%	L:\GROUP\PLANNING\fixedexp\01fixed\btm depr.wk4
Total Fixed (Group 40 for Functionals)	72,664.5	75,088.5	75,088.5	75,088.5	2,424.0	3.3%	
20 Total Cost Assignments Absorbed in Overh	42,244.5	40,081.1	40,081.1	40,081.1	-2,163.4	-5.1%	
Total Fixed/Overhead	114,909.0	115,169.6	115,169.6	115,169.6	260.6	0.2%	

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**PPD ALLOC/ SUMMARY  
FUNCTIONAL & C HEAD EXPENSE  
GROSS (\$000)**

Note: These charges are obtained from K. O'Rourke's group (PPD Div. FP&A; usually via Patty Kadish)

	1998 Total	% Increase	2000 AGU	2001 Plan	2001 APU	2001 AGU	% Increase	Notes
<b>Other Cost Expense Pools - Kevin O'Rourke (PPD Div. FP&amp;A)</b>								
Other taxes on purchases	63.5	0.0%	50.0	50.0	50.0	50.0	0.0%	
MFG Inventory Sales Tax	0.0	#DIV/0!	14.0	17.0	17.0	17.0	-24.3%	
Insurance other PP&E	207.9	0.0%	152.0	115.0	115.0	115.0	0.0%	
Insurance Auto/Truck	1184.0	0.0%	1.8	1.8	1.8	1.8	0.0%	
Cafeteria	1855.3	0.0%	1,200.0	1,219.0	1,219.0	1,219.0	-7.7%	
Security	888.4	0.0%	512.0	472.5	472.5	472.5	-2.8%	
Other Corp Admin	758.3	0.0%	0.0	0.0	0.0	0.0	-2.9%	
Subtotal - Corp Admin	4,857.4	0.0%	1,829.8	1,875.3	1,875.3	1,875.3	-2.9%	Journal Entry: Direct from CHMS by 6A132 CHMS** to PPRD 746-80
3 Satellite Copiers	904.0	0.0%	555.2	539.0	539.0	539.0	-20.7%	
3 Shuttle Bus	186.0	0.0%	111.0	134.0	134.0	134.0	-5.4%	
3 Mailroom	525.0	0.0%	314.0	297.0	297.0	297.0	2.7%	
7 CHMS -OSS Fixed Admin Svcs	546.0	0.0%	410.0	421.0	421.0	421.0	-1.3%	
Library Info Services	Internal	0.0%	2,820.0	2,764.0	2,764.0	2,764.0	7.2%	
Other Fixed from PPD Comm	131.0	0.0%	0.0	0.0	0.0	0.0	12.1%	Journal Entry: Direct from CHMS by 6P106 CHMS** to AS4
Subtotal Fixed from PPD Comm	2,292.0	0.0%	4,210.2	4,155.0	4,155.0	4,155.0	5.0%	Journal Entry: Direct from Jim Scully by 6D1R60** to AS4
3 Purchasing Fixed(CHMS)	1,670.0	0.0%	897.0	747.0	747.0	747.0	-0.6%	
6 Other Tele/Mail(CHMS) - MIS Telecomm	178.0	0.0%	116.0	130.0	130.0	130.0	0.0%	
10 PPD Mailroom (UPS)	110.0	0.0%	60.0	63.0	63.0	63.0	-6.6%	
Subtotal Fixed from CHMS & PPD Ops	1,958.0	0.0%	873.0	940.0	940.0	940.0	-3.7%	
Subtotal Other Cost Expense Pools	9,107.4	0.0%	7,013.0	6,970.3	6,970.3	6,970.3	-33.0%	
<b>Corp Admin Expense Assignments - Kevin O'Rourke (PPD Div. FP&amp;A)</b>								
3 LC Employment	130.0	0.0%	43.0	43.0	43.0	43.0	0.0%	
3 LC Skills Develop	21.0	0.0%	4.0	4.0	4.0	4.0	-6.6%	
3 Corporate Training	138.0	0.0%	61.0	57.0	57.0	57.0	0.0%	
3 LC Emp Skills Train College Relations	0.0	0.0%	0.0	0.0	0.0	0.0	0.0%	
Other Unit of Activity	321.0	0.0%	0.0	0.0	0.0	0.0	-3.7%	
Sub-Total Unit of Activity	610.0	0.0%	108.0	104.0	104.0	104.0	0.0%	
4 Outside Audit Fees	0.0	#DIV/0!	0.0	0.0	0.0	0.0	-33.0%	
4 Drug User Fees	1818.0	0.0%	1,802.0	1,207.0	1,207.0	1,207.0	8.7%	
1 Patents & Trademark	3819.0	0.0%	5,585.0	6,050.0	6,050.0	6,050.0	0.0%	
Other Pass Thru Charges	2761.0	0.0%	0.0	0.0	0.0	0.0	0.0%	
Sub-total Pass Thru Charge Basis	8398.0	0.0%	7,367.0	7,257.0	7,257.0	7,257.0	0.0%	
Corporate Licensing	726.0	0.0%	712.0	738.0	738.0	738.0	3.7%	
Account Payable	535.0	0.0%	352.0	343.0	343.0	343.0	-2.8%	
Legal Staff	2105.0	0.0%	1,907.8	2,306.0	2,306.0	2,306.0	20.9%	
Regulatory Affairs	342.0	0.0%	388.0	481.0	481.0	481.0	24.0%	
Payroll	593.0	0.0%	228.0	214.0	214.0	214.0	-0.1%	
General Ledger System	0.0	#DIV/0!	0.0	0.0	0.0	0.0	-3.0%	
Fixed Retainer Charge	1876.0	0.0%	1,303.0	1,263.3	1,263.3	1,263.3	9.3%	
Other Fixed Retainer	7940.0	0.0%	4,890.9	5,345.3	5,345.3	5,345.3	2.8%	
Sub-total Corp Admin Fixed	14,117.0	0.0%	12,365.9	12,706.3	12,706.3	12,706.3	0.0%	
Subtotal Corp Admin	23,125.0	0.0%	17,576.9	18,469.6	18,469.6	18,469.6	0.0%	
Key Check:			1,802.0	1,207.0	1,207.0	1,207.0	0.0%	
Overhead - Burden			0.0	0.0	0.0	0.0	0.0%	
Overhead - FDA Fees			0.0	0.0	0.0	0.0	0.0%	
Library Info Services charged to depts			19,378.9	19,675.6	19,675.6	19,675.6	0.0%	
Total Cost Pools & Assignments								

Key Check to verify subsequent schedules are picking up all these numbers.  
We estimate our own FDA costs because Corp gives us only 1 component.

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		2000														2001														98 Vs 99			
		Memo														98 Vs 99														Variances			
Div.	Dept.	780001	789100	790152	792410	794335	792007	790012	790300	794300	790012	790300	794300	790012	790300	794300	790012	790300	794300	Total	\$	%											
42	472	28.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	28.40	(0)	(0.00%)											
	Subtotal	28.40	0.80	0.80																28.40	(0)	(0.00%)											
44	47C		0.80																	0.80	(0)	(0.00%)											
	47T		0.20																	0.20	(0)	(0.00%)											
	405			0.00																0.00	(0)	(0.00%)											
	Subtotal	0.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.70	(-4.7)	#DIV/0!											
46	469	0.00	25.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.50	(-4.7)	(-470.00%)											
	Subtotal	0.00	25.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	25.50	(0)	(0.00%)											
47	4P8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	30.10	(-30.1)	#DIV/0!											
	4P7	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	30.10	(-30.1)	#DIV/0!											
	4P4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	51.67	(-51.7)	(-100.00%)											
	4P5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	51.67	(-51.7)	(-100.00%)											
	41M	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	91.50	(-91.5)	(-100.00%)											
	4R1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	153.67	(-153.7)	(-100.00%)											
	482	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	(0)	(0.00%)										
	Subtotal	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3,004.60	(-3,004.5)	(-100.00%)											
52	433	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.99	(-6.9)	(-100.00%)											
	Subtotal	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.99	(-6.9)	(-100.00%)											
53	491	71.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	71.10	(0)	(0.00%)											
	44F	71.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	71.10	(0)	(0.00%)											
	44J	71.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	71.10	(0)	(0.00%)											
	Subtotal	71.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	71.10	(0)	(0.00%)											
Total		99.50	26.50	0.00	187.10	328.70	2,031.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3,498.46	(-1,089.3)	(-45.25%)											
Reference		16.00	15.00	14.00	13.00	11.00	12.00	17.00	18.00	19.00	18.00	17.00	16.00	15.00	14.00	13.00	12.00	11.00	10.00	3,498.46	(-1,089.3)	(-45.25%)											

Note: These charges are obtained from various memos (mainly from PPD Ops). These memos are detailed in the Fixed Expenses binder. All PPD expenses come from Steve Szostak directly (these should be in line with what PPD Ops has submitted (via J. Trux)).

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## Fixed Allocations from Operations

(via J. Truax memo)

		2000	2001	PD Variances		RD Variances	
		Product Develop	Research & Develop	Product Develop	Research & Develop	\$	%
PD RD							
11	WISDOM(On-Going)	189,000	139,700	183,000	139,650	-6,000	-3.2%
	EDMS (On Going)	255,000		255,000			
	EDMS Project Expense	85,000		0			
12	a) D-44K Stability (DQF)	75,000	440,400	75,000	524,800	0	0.0%
12	24 CHEN Utilities	48,000	235,000	104,600	188,800	56,600	117.9%
12	26 CHEN Maintenance	208,000	947,000	472,000	899,000	264,000	126.9%
12	22 PA ABC Allocations	682,000	68,675	778,000	68,600	96,000	14.1%
12	27 QA ABC Allocations	978,000	1,438,000	1,320,000	1,942,000	342,000	35.0%
23	CAPD Warehouse/Waste		83,648		81,773	0	-2.2%
28	CAPD Project Exp. Transfer		105,000		105,000	0	0.0%
25	D-55A Engineering Support		268,000		375,000	0	39.9%
21	Corp. Eng. Proj. Expense		1,426,000		1,993,000	0	39.8%
12	D-55T Calibration Servic	40,000		40,000		0	0.0%
			0		0	0	
29	CHEN Envir Health & Saf	0	558,000	0	597,000	0	7.0%
	Total	2,560,000	5,709,423	3,227,600	6,914,623	667,600	26.1%
						1,205,200	21.1%

a) Not included in overhead; charged directly to projects.

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# ***Key Unfunded List***

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**PPD - Research and Development  
2001 PLAN  
Key Unfunded Projects  
(\$MM's)**

(As of 1/5/2001)

<u>Drug/Compound</u>	<u>Project Description</u>	<u>2001 PLAN</u>
<b>NEUROLOGY</b>		
Depakote	New Formulations (Epilepsy & Acute Migraine)	1.9
Depakote	Bipolar in Pediatric Mania	1.4
ABT-594	Post Milestone Funding (3rd and 4th Quarter)	9.8
ABT-594	Phase IIB Osteoarthritis Study (assumes 1/1/01 start date)	5.8
ABT-594	Additional Acute Pain Study (Phase IIB Molar Extraction Study)	3.0
COX-II	Ongoing Pre-Clinical Studies	3.0
ABT-089	Single/Multiple Rising Dose Phase I Study	7.0
ABS-103	Pre-Clinical Studies	3.3
ABS-103	Single Rising Dose Phase I Study	2.4
NPS-1778	Pre-Clinical Studies	3.7
NPS-1778	Single and Rising Multiple Phase I and Formulation Bio Studies	2.4
<b>Subtotal NEUROLOGY</b>		<b>43.7</b>
<b>ANTI-INFECTIVE</b>		
Clarithromycin	Asthma/Immunomodulatory Studies	2.4
ABT-773	ABT-773 IV Development Cost	8.0
Quinolone (ABT-492)	Phase II Acceleration/Expansion of Clinical Studies	9.7
Quinolone (ABT-492)	I.V. Formulation	4.0
Quinolone (ABT-492)	Japan Phase I Study	1.0
Omnicef	Pharyngitis/Tonsillitis Study: Pediatrics, Suspension, 5D BID vs. Zithromax	4.0
Omnicef	ABEC8 - Two Arm Study 5D QD vs. Comparator	2.4
<b>Subtotal ANTI-INFECTIVE</b>		<b>31.5</b>
<b>UROLOGY</b>		
Fenofibrate	Diabetics	4.0
Bimoclomol	Phase III Studies	10.0
KCO	Pre-Clinical/Phase I Studies	8.0
<b>Subtotal UROLOGY</b>		<b>20.0</b>
<b>HIV/IMMUNOLOGY</b>		
Kaletra	Phase IIB Program (unfunded portion)	5.6
Kaletra	Kaletra QD	4.2
Kaletra	Post Approval Commitments	4.2
Kaletra	Kaletra Salvage	2.8
Kaletra	Kaletra Firstline	2.6
Kaletra	Expanded Access Program	1.6
Kaletra	Phase IV RTI	1.3
Kaletra	IBHSC Cdrom	1.0
Kaletra	Metabolics Program	0.8
Kaletra	Miscellaneous Phase IV Studies	0.7
<b>Subtotal HIV/IMMUNOLOGY</b>		<b>24.8</b>
<b>ONCOLOGY</b>		
ABT-627	Early Stage Pca Cancer	11.0
K-5	Pre-Clinical/Phase I Studies	8.8
<b>Subtotal ONCOLOGY</b>		<b>19.8</b>
<b>DISCOVERY</b>		
DDC's	Development of DDC's	7.7
<b>IN-LICENSED COMPOUNDS</b>		
Various	Funds to Acquire New Compounds	7.7
<b>PRODUCTIVITY</b>		
30% Reduction in Capital	Productivity Projects	6.0
	Rosetta Gene Expression	
	Genomics/HTS Expansion Program	
	AEGIS MedDRA	
<b>Total Unfunded 2001 PLAN</b>		<b>145.0</b>





## Abbott Portfolio Review

March 7-9, 2001

- 
- Project: NNR
  - Compound: ABT-594
  - Presenter: Bruce McCarthy, MD

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## ABT-594 Project Team Members

- |                    |  |
|--------------------|--|
| ◆ Venture          | Bruce McCarthy, Michael Biarnesen,<br>Marilyn Collicott, Aldona Matalonis, Alyssa<br>O'Neill |
| ◆ Statistics       | David Morris, James Thomas, Yiming<br>Zhang  |
| ◆ Commercial       | Laura Robinson, Lisa Lux   |
| ◆ Pharmacokinetics | Walid Awni, Sandeep Dutta  |
| ◆ Discovery        | Mike Meyer, Jim Sullivan   |
| ◆ PARD             | Howard Cheskin, Lloyd Dias, David Stroz  |
| ◆ SPD              | Jim Ciullo   |
| ◆ Metabolism       | Joe Machinist, Stan Roberts  |
| ◆ Toxicology       | Bill Bracken, Julia Hui  |
| ◆ Regulatory       | Jim Steck, David Ross, Nigel Livesey   |

Revised 06/16/2001 1:18 PM JAB... in: Abbott presentation/BDM - 034291

### ABT-594 Target Indication

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

#### Upside Claims

- ◆ Neuropathic Pain
- ◆ Post herpetic neuralgia
- ◆ OA Pain
- ◆ Chronic Pain
- ◆ Cancer Pain

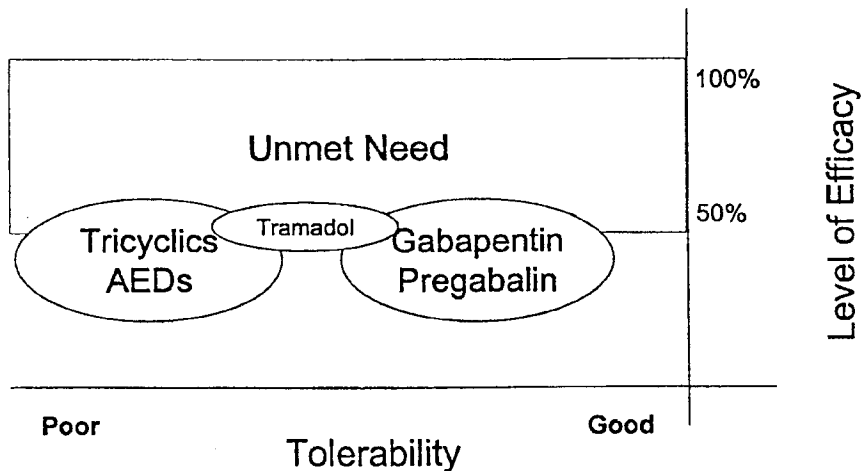
#### General Pain Claim

- ◆ Not viable due to 1.5 hour onset

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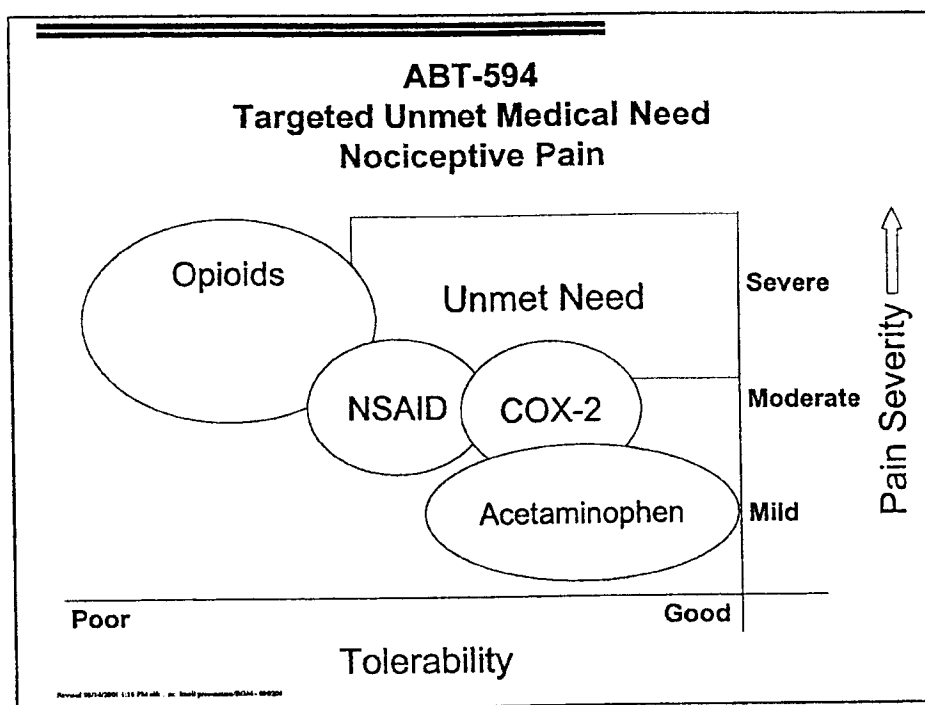
3

### ABT-594 Targeted Unmet Medical Need Neuropathic Pain



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**ABT-594**  
**Targeted Product Profile**

	ABT-594 TARGET PROFILE	Current Gold Standard Gabapentin (Neurontin)
Efficacy	> 40% Average Pain Reduction	39% Average Pain Reduction
Side Effects	< 20% Nausea, Vomiting, Dizziness (during titration)	Somnolence: 23% Dizziness: 24% Confusion: 8% Nausea: 8%
Dosing	BID	TID
Other		Not Labeled for Pain

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## ABT-594

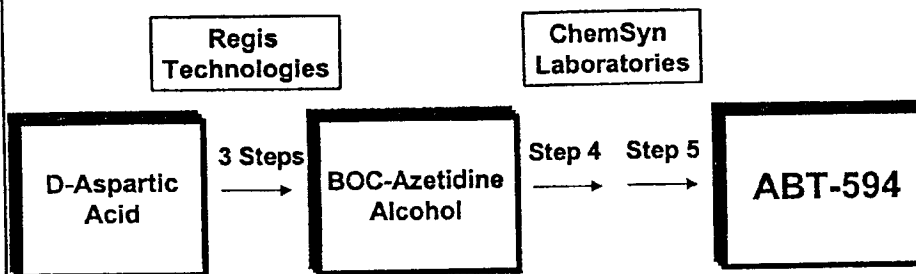
### ◆ Key pre-clinical findings:

- Pharmacology
  - Effective across preclinical models of acute, persistent and neuropathic pain
  - Retains efficacy upon repeated dosing
  - Analgesia via activation of neuronal nicotinic receptors (NNRs) and not via opioid receptors
  - Morphine-like side effects unexpected
    - Constipation
    - Respiratory depression
    - Sedation
- PK/metabolism in animals
  - No CYP interaction
  - No significant metabolism
- Toxicology
  - No issues identified

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1

## ABT-594

### ◆ Chemistry and Manufacturing: Drug Substance (Ebanicline Tosylate)



Commercial Cost Estimate: \$20,000 / Kg Tosylate Salt  
(\$40,000 / Kg Base Equivalent)

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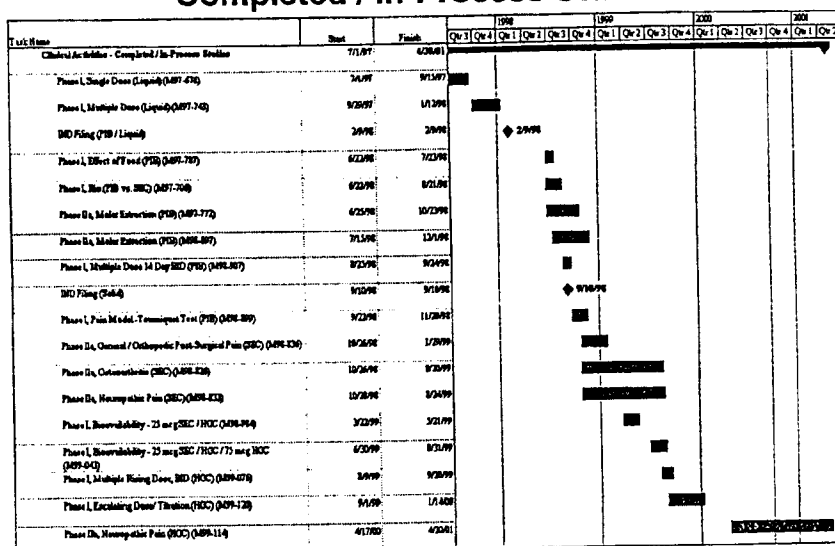
## ABT-594

### ◆ Chemistry and Manufacturing: Drug Product

- Hard Gelatin Capsules
- Dosage strengths: 75, 150, (25)  $\mu$ g Base eq.
- Site: Abbott Puerto Rico
- Manufacturing process:
  - Drug is dissolved in hydro-alcoholic solution
  - Solution sprayed onto micro-porous excipient in a high-shear mixer
  - Granulation is dried, blended with excipients and encapsulated into hard gelatin capsules

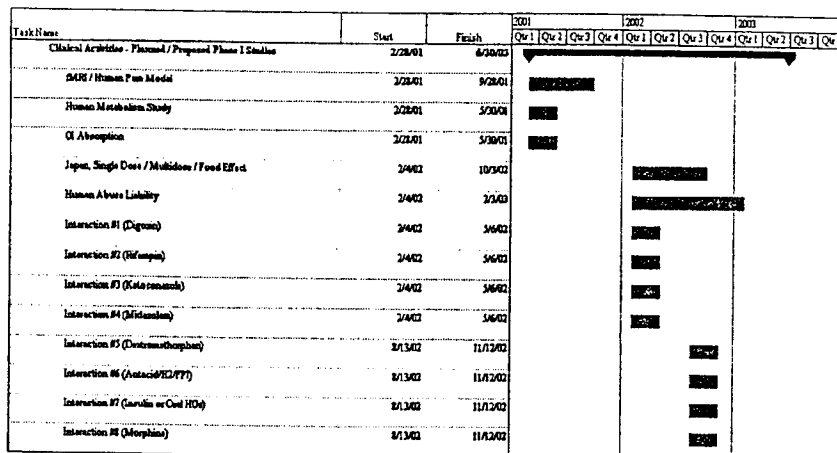
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## ABT-594 Global Clinical Development Plan Completed / In-Process Studies



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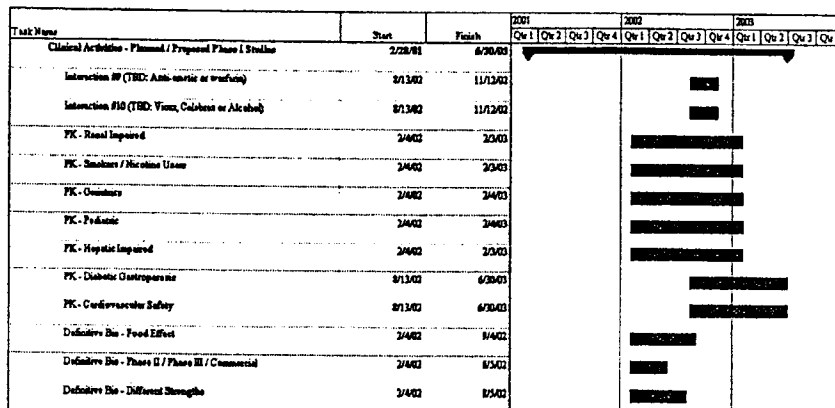
## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 1 of 2



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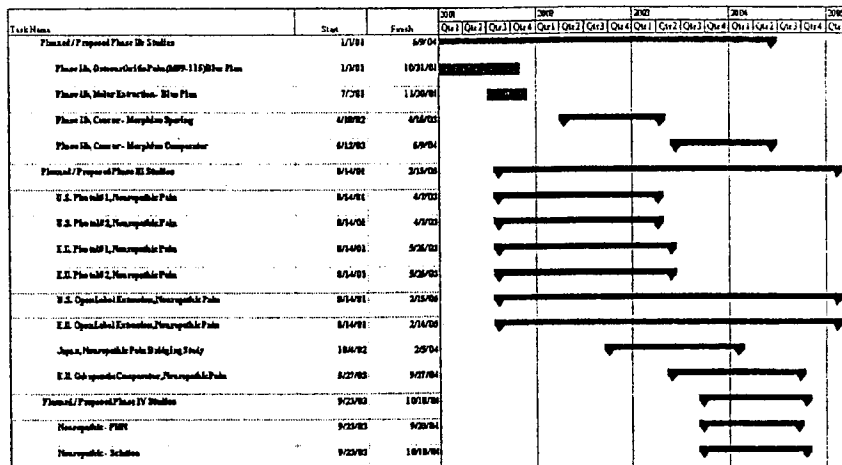
## ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies, Gantt 2 of 2



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## ABT-594 Global Clinical Development Plan Planned & Proposed Phase II, III & IV Studies



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## ABT-594 Development Budget

(\$MM)	2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
<b>Base Program</b>						
CMC						
- PARD	1.1	2.8	6.2	5.2	3.2	1.0
- SPD	0.1	1.0	1.0	1.0	1.0	1.0
Drug Safety	1.4	0.9	2.3	1.7	0.9	0.5
Other:	1.2	0.5	1.2	-	-	-
<b>Base Program Total</b>	<b>3.8</b>	<b>5.2</b>	<b>10.7</b>	<b>7.9</b>	<b>5.1</b>	<b>2.5</b>
<b>Clinical Program</b>						
Venture Management	4.0	0.2	6.6	6.6	6.0	5.0
Data Mgmt / Stats	0.5	0.2	5.5	7.5	4.7	2.0
Clinical Grants	1.1	0	36.8	33.7	6.0	2.0
<b>Clinical Program Total</b>	<b>5.6</b>	<b>0.4</b>	<b>48.9</b>	<b>47.8</b>	<b>16.7</b>	<b>9.0</b>
<b>Annual Total Costs</b>	<b>9.4</b>	<b>5.6</b>	<b>59.6</b>	<b>55.7</b>	<b>21.8</b>	<b>11.5</b>

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## ABT-594

### ◆ Summary of Phase I findings

- Half-life ( $t_{1/2}$ ): 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{max}$  similar with/without food
- $T_{max}$  may vary somewhat with formulation, food
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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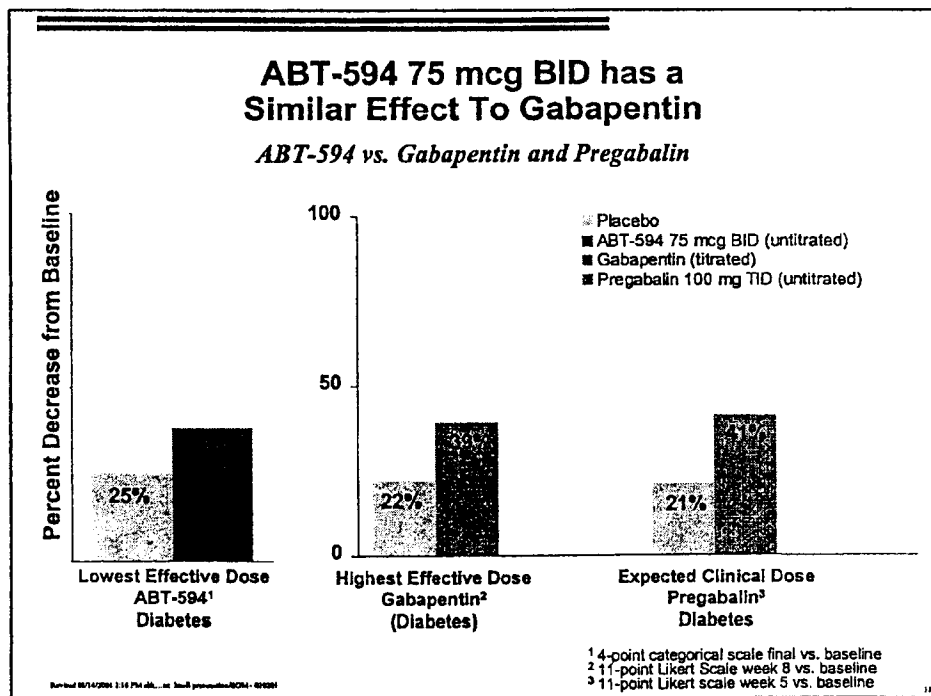
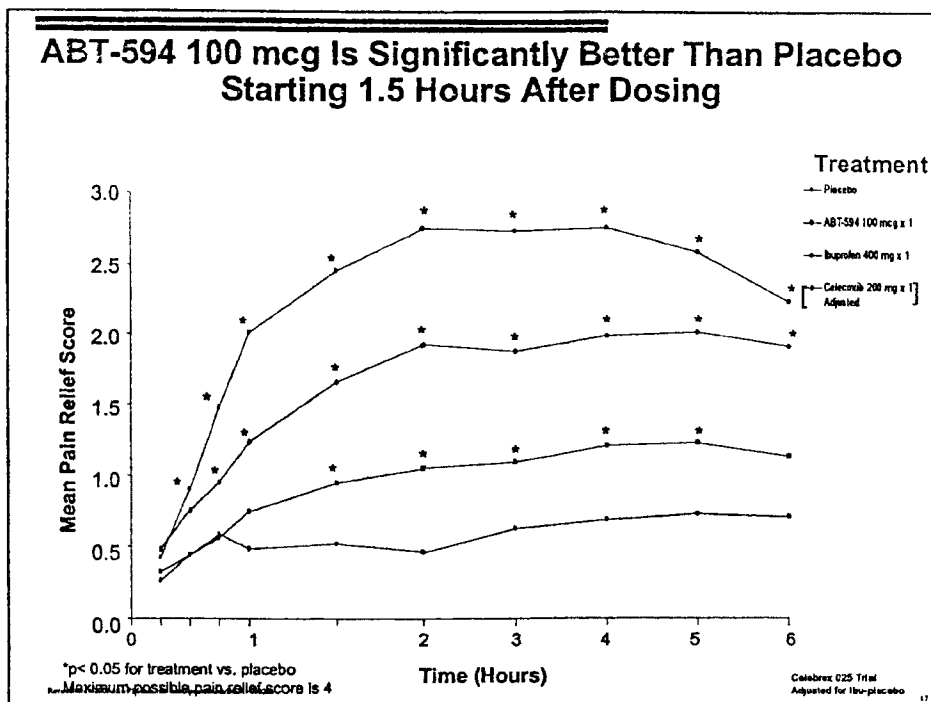
## ABT-594

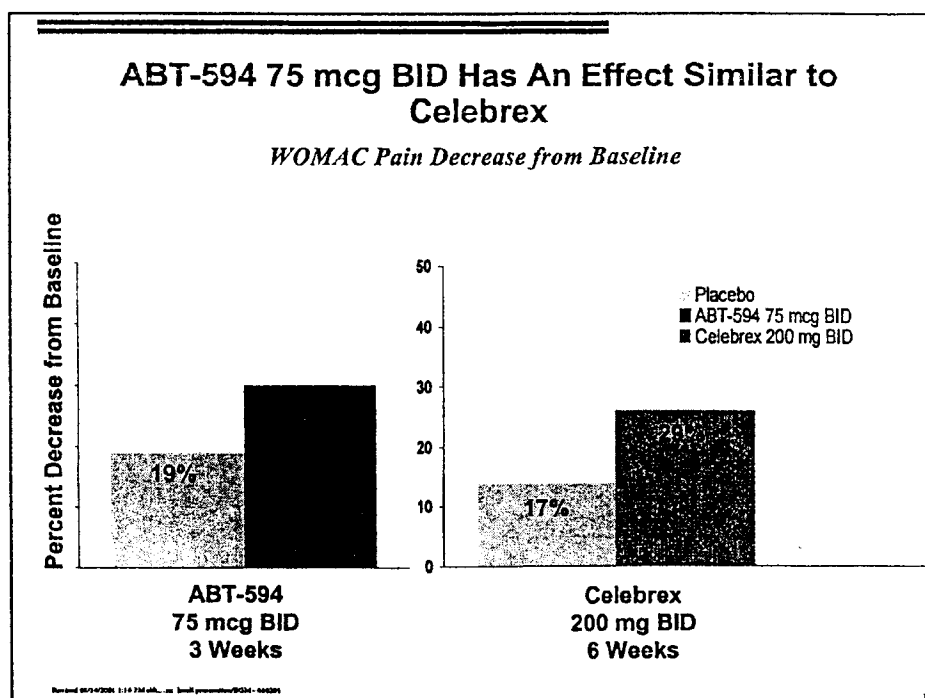
### ◆ Summary of Phase IIa findings

- ABT-594's analgesic potential demonstrated in:
  - Molar Extraction
  - Neuropathic Pain
  - Osteoarthritis
- Well tolerated in chronic Phase IIa studies
  - 75 mcg BID maximum dose
- Limited additional Phase I data suggested re-evaluation of efficacy at higher doses

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### Adverse Event Rates for ABT-594 and Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

<sup>1</sup> Max, 1987 (n=29)

<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

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### Adverse Event Rates for ABT-594 and Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

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### ABT-594

#### ◆ Summary of Phase IIb Plans

- Neuropathic Pain
  - Improved study design
  - 150, 225, 300 mcg BID
  - Data available 5/2001
- Osteoarthritis
  - Blue plan
- Tolerability evaluation
  - Rate of rise impact
  - Titration

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## ABT-594

### ◆ Regulatory status:

- USA, Canada
  - IND 56,980, solid oral dosage form - Division of Anesthetic, Critical Care, and Addiction Drug Products (1998)
  - IND 55,293, oral solution - Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (1998)
  - Informal Teleconference with FDA, August 26, 1998 (incl. John Hyde, MD)
  - End of Phase II meeting planned, October 2000
- Europe
  - Phase I studies conducted, no regulatory interactions
  - End of Phase II meeting planned, October 2001
- Japan
  - No activity

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## Strategic Summary

## ABT-594

### ◆ Key Project Strengths / Positives

- Product attributes
  - Orally available
  - May be effective for neuropathic and nociceptive pain
  - Preclinical promise: morphine-like efficacy
    - Not associated with opioid liabilities, including sedation, respiratory depression, constipation, addiction
  - No currently approved drugs for diabetic neuropathic pain
- Technology/innovation
  - Novel mechanism: NNR
- Time to market
  - Launch 4Q/2004
- Business franchise strength: Emerging
  - Strength in hospital channel (HPD)
  - Strength in neurology (neuropathic pain)
  - Leverage community strength

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Strategic Summary

## ABT-594

◆ **Potential Issues / Threats / Negatives**

- Tolerability issues
  - Nausea, vomiting, dizziness
- Manufacturing/cost of goods
  - Potent Drug
- Efficacy
  - Therapeutic index
- Clinical recruitment
  - Neuropathic pain: evolving clinical research environment
  - Nociceptive pain: mature clinical research environment
- Regulatory risk
  - Neuropathic pain
    - Lack of precedent is threat (more difficult) and opportunity (first mover)
    - Large unmet need may facilitate

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Strategic Summary

## ABT-594

◆ **Key Decisions**

**ANNUAL TOTAL COSTS (\$MM)**

2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
9.4	5.6	59.6	55.7	21.8	11.5

Go/No Go  
6/2001

US/EMEA  
Filing  
9/2003

Japan Filing  
9/2004  
  
 US/EMEA  
Launch  
9/2004

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**ABT-594****Strategic Summary****◆ Proposed Action Plans****Strategic Analyses**

- Overall pain strategy
  - Abbott
  - Mechanistic and therapeutic diversity and depth to achieve success
  - Currently available assets, including ABT-594
- ABT-594 and NNRs for pain
  - Separation of adverse events and efficacy
    - Pharmaceuticals
    - Titration
    - Pharmacological
  - Oral absorption kinetics
    - Basis of prolonged  $T_{max}$
    - Means to improve (shorten)  $T_{max}$
    - Implications of shortened  $T_{max}$
  - Go/No Go ABT-594
    - 6/2001

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**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Wednesday, March 7**

7:30 am	Welcome/ introduction	10 min		J. Leiden
7:40 am	Meeting objectives	10 min		J. Leonard
	<b>Anti-Infectives</b>	<b>Presentation</b>	<b>Discussion</b>	
	Quinolones			
7:50 am	- ABT- 492	20 min	5 min	C. Craft
8:15 am	- HSR- 903	30 min	10 min	T. Hirose/R. Krautheimer
	<b>Anti-virals</b>			
8:55 am	Triangle projects	30 min	10 min	M. Heath-Chiozzi
	- HIV and HBV (FTC; DAPD)			
9:35 am	<b>Morning Break</b>			
	<b>Urology</b>			
9:55 am	BSF 420627 (ETA/ BPH)	30 min	10 min	M. Kirchengast
	<b>T3/T4</b>			
10:35 am	T3/T4	15 min	5 min	C. Schreiber/T. Miller
	<b>Asthma</b>			
10:55 am	Hokunalin tape	15 min	5 min	T. Hirose/R. Krautheimer
	<b>Oncology</b>			
11:15 am	ABT-510	20 min	15 min	P. Nisen
11:50 am	ABT-751	20 min	15 min	P. Nisen
12:25 pm	<b>Lunch</b>			
1:25 pm	ABT-518	15 min	5 min	P. Nisen
1:45 pm	Rubitecan	20 min	5 min	P. Nisen
2:10 pm	Theragyn	20 min	5 min	P. Nisen
2:35 pm	ABT-627	30 min	10 min	P. Nisen
3:15 pm	<b>Afternoon Break</b>			
	<b>Cardiology</b>			
3:35 pm	Darusentan	45 min	10 min	M. Luz/M. Kirchengast
	(LU 135252)			
	LU208075			M. Luz/M. Kirchengast
	<b>Thrombosis</b>			
4:30 pm	PEG-hirudin	30 min	10 min	V. Ifthekar/U. Legler
5:10 pm	Ancrod	30 min	10 min	D. Levy/U. Legler
5:50 pm	Urokinase/ Pro-urokinase	30 min	10 min	S. Guptha

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Thursday, March 8**

Neuroscience		Presentation	Discussion	
7:30 am	ABT 594	30 min	10 min	B. McCarthy
8:10 am	ABT-963	15 min	15 min	Granneman/Doan/Bell
8:40 am	BSF 201640	30 min	10 min	B. Rendenbach-Mueller
9:20 am	BSF 74398 (Parkinson)	30 min	10 min	S. Dawe
10:00 am	Morning Break			
10:20 am	Dilaudid OROS	45 min	15 min	B. Gold/R. Krautheimer
11:20 am	BSF 190555 (Schizophrenia)	30 min	10 min	B. Rendenbach-Mueller
12:00 pm	Lunch			
1:00 pm	Hydrocodone	10 min	10 min	S. Collins
1:20 pm	Bimocloamol ( ABT-822)	30 min	10 min	B. Wallin
Gastro-enterology				
2:00 pm	Ganaton (pro-kinetic)	15 min	5 min	S. Dawe/R. Krautheimer
2:20 pm	TU-199 (proton pump inh.)	30 min	10 min	T. Hirose/ R. Krautheimer
3:00 pm	AU - 224 (colon pro-kinetic)	20 min	5 min	T. Hirose/ R. Krautheimer
3:25 pm	Afternoon Break			
Phase III Projects				
3:45 pm	ABT-773	30 min	15 min	C. Craft
4:30 pm	D2E7	45 min	30 min	C. Spiegler/E. v. Borcke

**Portfolio Review Meeting  
March 7 – 9, 2001  
The Hyatt Deerfield**

**Friday, March 9**

**Phase III Projects (cont'd)**

		<b>Presentation</b>	<b>Discussion</b>	
7:30 am	Segard	45 min	15 min	L. Daum/T. King
8:30 am	J695	30 min	10 min	R. Janocha/T. King
9:10 am	Clivarine	30 min	15 min	F. Misselwitz/S. Schaeffer
9:55 am	<b>Morning Break</b>			
10:15 am	Rythmol SR	30 min	15 min	A. Pethö-Schramm/E. Schneider
11:00 am	Levosimendan	30 min	15 min	C MacLeod

**Phase IV Projects**

11:45 am	Clarithromycin	15 min	5 min	C. Olson
12:05 pm	Omnicef	15 min	5 min	C. Olson
12:25 pm	<b>Lunch</b>			
1:25 pm	Kaletra	15 min	5 min	E. Sun
1:45 pm	Norvir	15 min	5 min	E. Sun
2:05 pm	Meridia ( Sibutramine )	15 min	5 min	E. Chong/W. Hargan
2:25 pm	Uprima	15 min	5 min	S. Bukofzer
2:45 pm	Trandolapril (patch, intervention trials)	15 min	5 min	B. Rendbach-Mueller/ U. Legler/N. Bender
3:05 pm	<b>Afternoon Break</b>			
3:25 pm	Fenofibrate	15 min	5 min	D. Yannicelli
3:45 pm	Depakote	15 min	5 min	K. Sommerville
4:05 pm	Gengraf	15 min	5 min	T. Japour
4:25 pm	<b>Conclusion</b>			Jeff Leiden



# Abbott Portfolio Review

March 7-9, 2001

- Project/Compound: **ABT-773 Adult Oral Tablet**
- Presenter: **Dr. Carl Craft**
- Project Team Members : **Carol Meyer, Rod Mittag**

## ABT-773 Target Product Profile

- **Target Indication:**
  - Respiratory tract infections
- **Targeted unmet medical need:**
  - Activity against resistant organisms
  - Low propensity for resistance development
  - Convenient dosing
  - Very good tolerability
  - Insignificant drug-drug interactions
- **Targeted profile vs gold standard**

	ABT-773	Blaxin XL	Zithromex
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d	250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP
Efficacy	ABECB: 85% Cure, 88% Erad ABS: 82% Cure, 83% Erad CAP: 84% Cure, 91% Erad Pharyngitis: No clinical data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad	Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image
Adverse Events	Taste perversion: 4% Diarrhoea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhoea: 5% Nausea: 3% Vomiting: 1%	Very well tolerated; GI disturbance ~ 2-5%; no taste perversion
Resistance Claim	Being pursued	Under exploration	None

**HIGHLY  
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ABBT 0013203

### ABT-773 Key Pre-Clinical Findings

- **Toxicology:**
- Rat:** Target organs : liver, lung, testes, epididymides  
NTEL in rat  $\approx$  3.5 -8 x clin AUC
- Monkey:** Target organ: liver  
NTEL in monkey  $\approx$  1.5 -4 x clin AUC; Next higher dose of 50mg/kg only showed mild ALT elevation (7 -18 x clin AUC)
- Male fertility** NTEL  $\approx$  2-5 x clin AUC, although next higher dose had effects on sperm concentration and motility, these were reversible within 2 mo.

### ABT-773 Key Pre-Clinical Findings

- **Pharmacology:**
- ABT-773 dose-dependently prolonged canine Purkinje fiber repolarization in the absence of plasma protein binding at 5 mcg/mL (10x therapeutic)
  - In the presence of plasma proteins, a concentration of 5 mcg/ml was cleared but 50 mcg/mL was not. (100x therapeutic).
  - In anesthetized dogs, Abbott-195773 produced no significant effect on the corrected QT interval at concentrations up to  $8.86 \pm 0.27$  mcg/ml.
  - As plasma levels increased from  $8.86 \pm 0.27$  to  $22.00 \pm 0.61$  mcg/ml, QTc increased by  $40 \pm 2$  msec or  $11 \pm 1\%$ .
  - Studies in telemetry-instrumented dogs will be completed by May 1, 2001.

HIGHLY  
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### ABT-773 Key Pre-Clinical Findings

- **Metabolism:** Substrate and inhibitor of Cyp 3A (liver/GI)  
Clearance predominantly by hepatic metabolism in dog and rat  
Absolute bio about 36-60% (4 species)  
One metabolite (N-desmethyl) less active than parent

### ABT 773 Microbiology

- Unique mechanism, ribosome binding properties
- Active vs. key respiratory pathogens including macrolide-resistant streptococci
  - Among most active agents for Gram+ pathogens; more active than Aventis' telithromycin
  - Comparable activity to azithromycin/telithromycin for H. influenzae; weakness vs quinolones
- Bactericidal
- Extended post-antibiotic effect (PAE)
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome

MIC90	clarithromycin	trovafloxacin*	telithromycin	ABT-773
S. Pneumoniae (susc)	< 0.03	0.125	0.008	< 0.002
S. Pneumoniae (mef)	8.0	0.125	1	0.12
S. Pneumoniae (erm)	> 32	0.125	0.12	0.01
S. Pyogenes (mef)	16	0.125	1	0.12
S. Pyogenes (erm)	> 32	0.25	> 8	0.5
M. catarrhalis	0.03	0.015	0.25	0.25
H. influenzae	8	0.015	2	2

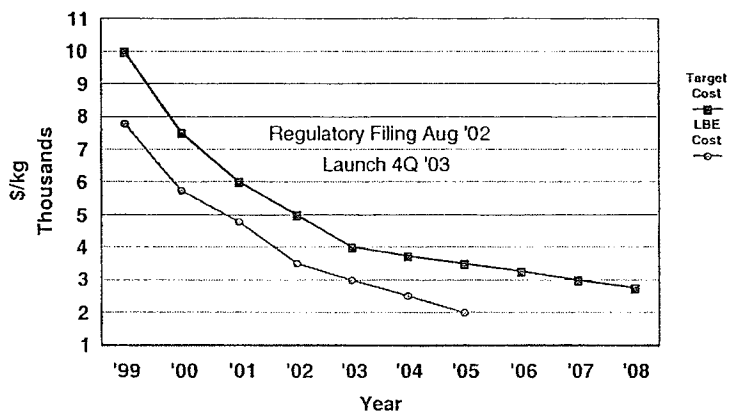
\* Withdrawn from market, but among the more potent quinolones

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## ABT 773 Chemistry and Manufacturing

### • Bulk Drug Substance

Cost of Goods based on Current Process



## ABT 773 Chemistry and Manufacturing

### • Drug Product

#### > Description:

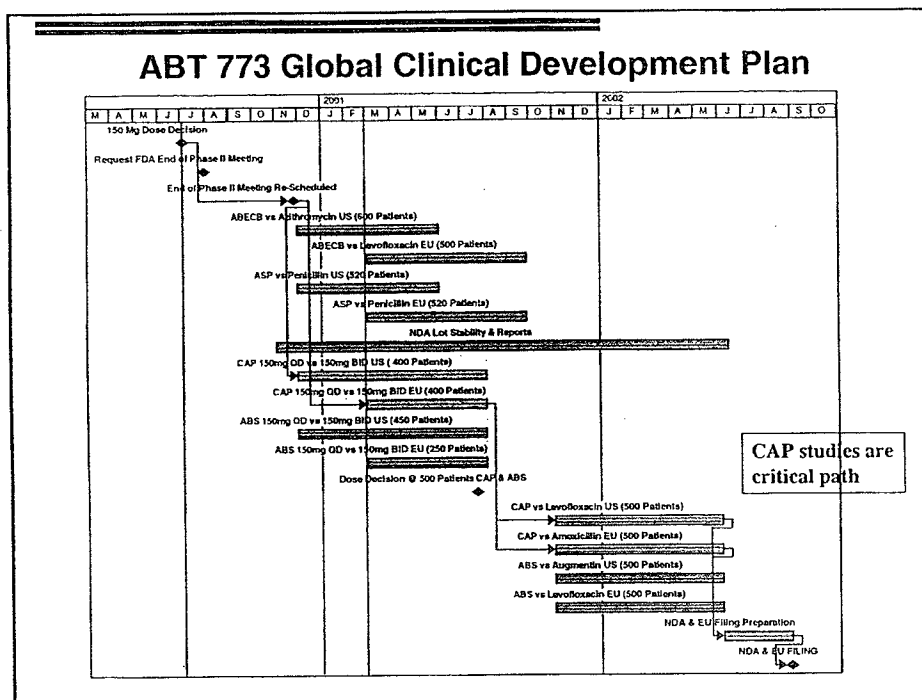
- Immediate Release 150mg Coated Tablet
- Commercial Product will be Global
- Planned Source US and UK

#### > Status:

- Intermediate Scale Product bioequivalent to Registration Lots
- Registration Lots used for Phase 3 studies
- Registration Lot Stability Studies initiated 2/01
- Final US and UK Scale up activities ongoing

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### ABT 773 TABLET BUDGET

	1997 Phase I	1998 Phase I	1999 Phase I/II	2000 Phase II/III	2001 Phase III	2002 to NDA Phase III	Total
Clinical Program	0.5	2.0	11.9	34.5	61.7	33.9	144.5
CMC	7.1	10.4	28.6	31.8	21.7	14.5	114.1
Drug Safety	1.0	2.5	2.5	3.0	1.9	1.0	11.9
Other	1.7	5.7	5.3	5.3	2.7	2.5	23.2
Total by Year	10.3	20.6	48.3	74.6	88.0	51.9	293.7
Cumulative	10.3	30.9	79.2	153.8	241.8	293.7	

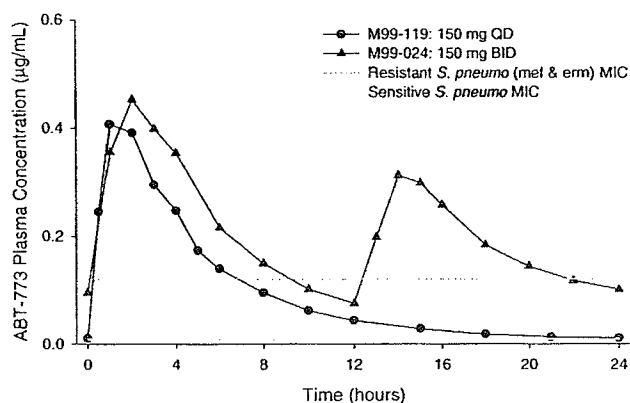
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### ABT 773 Phase I Findings

#### Pharmacokinetics

150 mg QD and 150 mg BID Profiles with *S. pneumo* MICs

H. flu MIC<sub>90</sub> is 2.0



### ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Clinical Response

	150 mg QD	300 mg QD	600 mg QD
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

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### ABT 773 Phase II Findings

#### Combined ABECB, CAP, ABS Bacteriological Response

##### Clinically and Bacteriologically Evaluable

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91%(29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84%(16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77%(37/48)
Overall	86% (49/57)	90% (84/93)	83%(82/99)

### ABT 773 Phase II Findings

#### Combined ABECB, CAP, ABS Adverse Events

##### All Adverse Events

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
<b>GI and Taste</b>			
Taste Perversion	4% (8/223)	17% (55/322)	27% (87/318)
Diarrhea	10%(22/223)	11% (34/322)	19% (60/318)
Nausea	5% (12/223)	12% (40/322)	26% (83/318)
Vomiting	2% (4/223)	6% (19/322)	14% (44/318)

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ABBT 0013209

### ABT 773 Indications

Infection	Dosage	Duration
Pharyngitis/Tonsillitis due to:		
<i>S. pyogenes</i> *	150 mg QD	5 d
Acute bacterial sinusitis due to:		
<i>H. influenzae</i>	150 mg QD or BID	10 d
<i>M. catarrhalis</i>	150 mg QD or BID	10 d
<i>S. pneumoniae</i> **	150 mg QD or BID	10 d
Acute bacterial exacerbation of chronic bronchitis due to:		
<i>H. influenzae</i>	150 mg	5 d
<i>H. parainfluenzae</i>	150 mg	5 d
<i>M. catarrhalis</i>	150 mg	5 d
<i>S. pneumoniae</i> **	150 mg	5 d
Community-acquired pneumonia due to:		
<i>C. pneumoniae</i>	150 mg QD or BID	10 d
<i>H. influenzae</i>	150 mg QD or BID	10 d
<i>L. pneumophila</i>	150 mg QD or BID	10 d
<i>M. pneumoniae</i>	150 mg QD or BID	10 d
<i>S. pneumoniae</i> **	150 mg QD or BID	10 d

\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.

### ABT-773 Phase III Clinical Plan

- **ABECB/ASP comparative studies 150mg QD**
  - Plan to complete in 2000/2001 season
  - Not on critical path to Aug 2002 filing
- **CAP/ABS Dose Ranging 150mg QD vs 150mg BID**
  - Dose selection July 2001 (500 patients per indication)
  - Meet U.S. open-label study requirement for approx. 80-100 bacteriologically evaluable subjects per indication (continue to 800/600 respectively if needed)
- **CAP/ABS comparative studies with selected dose**
  - Initiate Nov 2001 (2 studies each indication, 500 patients/study)
  - 2001/2002 season Northern Hemisphere

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### ABT 773 Phase III Clinical Plan

#### Studies starting in Fall 2001

Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Quinolone	250	EU (Non-IND)

### ABT 773 Regulatory Status

Region	Proposed Submission Date	Comments
US	August 2002	
Europe	August 2002	Centralised filing vs Mutual recognition strategy TBD based on strength of the Phase III data
Canada	August 2002	
Japan	TBD	Bridging strategy dependent on Ph I results in Japan and Kiko agreement

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## Strategic Summary

**ABT 773 Key Project Strengths / Positives**

- Excellent activity against key resistant respiratory pathogens
- Unique mechanistic advantages (ribosome binding properties)
- Low potential for resistance development
- Market expansion ex-US
- Represents a hedge against Biaxin IR patent expiration in 2004-2005
- Potential for I.V. formulation, expands scope of franchise into new market segment

## Strategic Summary

**ABT 773 Potential Issues/Threats/Negatives**

Key Issue	Potential Impact
Potential for class labeling regarding QT Prolongation effects	Reduced market share due to perceived safety issues
Obtaining enough resistant organisms in clinical trials for a resistance claim in product labeling, also FDA desire for severe bacteremic patients	Would need to rely solely on <i>in vitro</i> resistance data for product positioning, potential need for an IV formulation to obtain data on severe patients to support the claim
IV Formulation	Need IV formulation to strengthen strategic, commercial, and technical value of product
QD vs BID dosing impact on US and ex-US markets	Significant commercial hurdle in the U.S., relatively minor impact ex-US. QD may receive regulatory challenge ex-US; BID dosing has large negative impact on US sales
Delayed Phase III program due to delayed FDA EOP II meeting and weak flu season slowing CAP enrollment	Delay to dose selection decision beyond July/Aug 2001 could delay filing

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### ABT-773 Action Plans

Key Issue	Action Plans
Potential for class labeling regarding QT Prolongation effects	<ul style="list-style-type: none"> <li>Conduct EKG monitoring in Phase III to gather additional data on QT prolongation</li> <li>Pursue FDA request for Phase I study in cardiac impaired patients</li> <li>Conduct additional dog tox work to evaluate QT</li> </ul>
Obtaining enough resistant organisms in clinical trials for a resistance claim in product labeling, also FDA desire for severe bacteremic patients	<ul style="list-style-type: none"> <li>Target patient enrollment to obtain necessary organisms</li> <li>IV formulation would access bacteremic patients</li> </ul>
IV Formulation	<ul style="list-style-type: none"> <li>Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding</li> </ul>

### ABT-773 Action Plans

Key Issue	Action Plans
QD vs BID dosing impact on US and ex-US markets	<ul style="list-style-type: none"> <li>Select dose based on outcome of current QD vs BID trials</li> <li>Minimize regulatory risk</li> <li>Optimize global commercial opportunity</li> </ul>
Delayed Phase III program due to delayed FDA EOP II meeting and weak flu season slowing CAP enrollment	<ul style="list-style-type: none"> <li>CAP Study sites increased in the US and Europe from 209 to 300 sites</li> <li>Closely manage European site initiations to speed enrollment</li> <li>Implemented investigator incentives</li> <li>Other contingency plans</li> </ul>

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## Strategic Summary

**ABT 773 Contingency Plans**

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
  - Dose decision delayed to Sept 2001, filing delayed until Dec 2002
  - Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere
- Other Filing contingencies have been evaluated and are less desirable (regulatory, commercial, logistic)
  - **Option 1:** File Aug 2002 with ABECB/ASP/ABS indications, File Aug 2003 with CA P indication
  - **Option 2:** File in Aug 2002 ABECB/ASP 150mg QD, CAP/ABS 150mg BID
  - **Option 3:** File Dec 2002, all indications, Run 3-arm CAP comparative studies 2001/2002 season
  - **Option 4:** File Aug 2002, Run separate Phase III clinical programs in the U.S. and Europe for CAP and ABS, QD in US, BID ex-US

## Strategic Summary

**ABT 773 Key Decisions**

- A dose decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on Phase III data by July 2001
- CAP study enrollment is critical path to dose decision milestone
- Delay to dose decision will delay Phase III comparative study initiation currently planned for Nov 2001 and Aug 2002 filing
- Proposed budget (\$MM)

Thru 2000	2001	2002 to filing	TOTAL
153.8	88.0	51.9	293.2

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# **ABT-773 Update March 19, 2001**

## **Agenda**

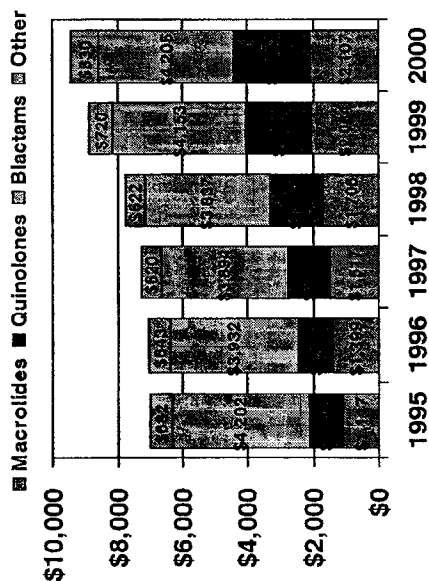
- **Market and trends**
- **Molecule**
- **Microbiology**
- **Pharm/tox**
  - **QT prolongation**
  - **Hepatotoxicity**
- **Clinical development**
  - **Phase I/II summary**
  - **Dose selection**
  - **Phase III program**
  - **Contingency plans**
- **Timeline and budget**
- **IV formulation**
- **Summary of key issues and action plans**

## Market and Drivers

- Infectious disease accounts for 13.3 million deaths yearly worldwide, 25% of all deaths
- Antibiotics are the 2<sup>nd</sup> most commonly prescribed category of drugs
- The global antibiotic market is a \$21B market, the 5<sup>th</sup> largest global market in sales
- The global antibiotic market has shown modest sales growth
  - 3.9% CAGR<sub>96-00</sub> in sales for overall combined market
  - 4.7% CAGR<sub>96-00</sub> in sales for branded combined market
- Sales growth in the U.S. has been driven by replacement of older generic agents with newer branded agents (most other markets show increasing generic use)
  - Antibiotic resistance results in OBSOLESCENCE of existing agents over time (a CHRONIC problem)
  - Sales per TRX rose from \$18.42 in 1995 to \$28.05 in 2000 (8.8% CAGR)
  - Generics still represent 61% of TRX, representing an opportunity for conversion
- Generics have been more stable ex-U.S

# U.S. Market Trends

## By Class

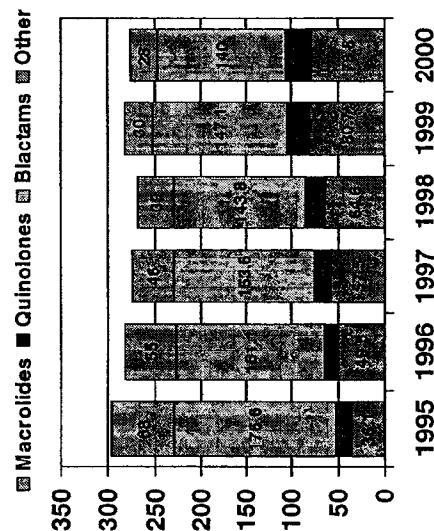


**SALES**

CAGR<sub>95-99</sub>: 6.1%

10.0% Branded

-5.5% Generic



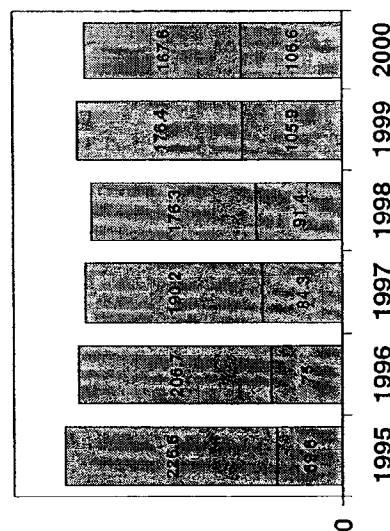
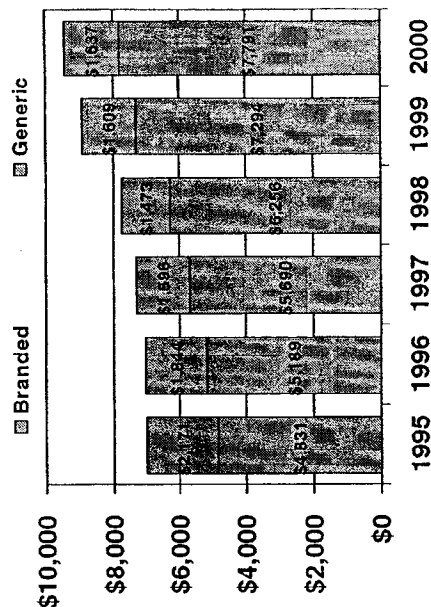
**TRX**  
(excludes IV)

CAGR<sub>95-99</sub>: -1.5%

8.9% Branded

-5.9% Generic

## Generic vs Brand



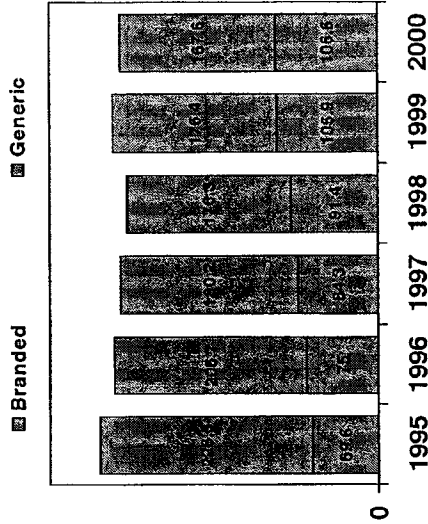
Macrolides and quinolones have driven the growth of the market

Generic use decreasing with increasing antibiotic resistance

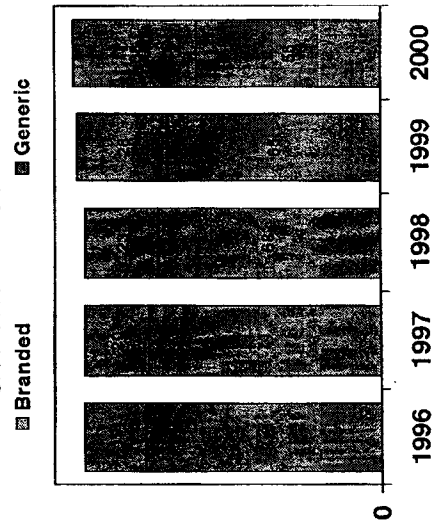
While most markets tend toward increasing utilization of generics, the antibiotic market is tending toward decreasing utilization of generics-OBSOLESCENCE

## Backup

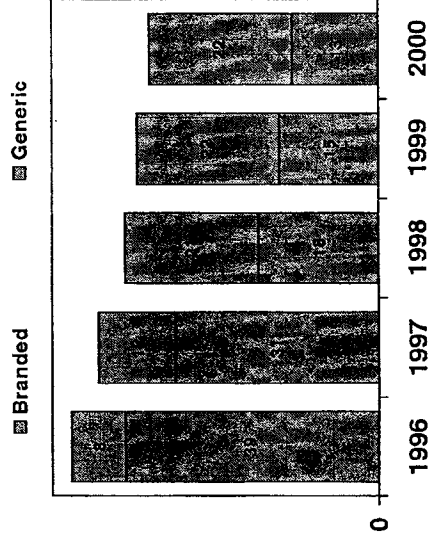
**Antibiotics**  
Brand: +9%  
Generic: -6%



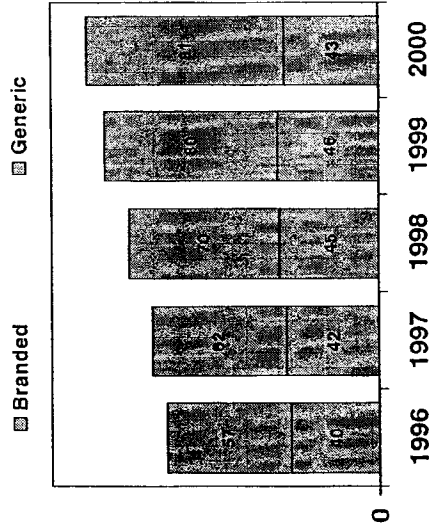
**Calcium Blockers**  
Brand: -6%  
Generic: +19%



**H2 Antagonists**  
Brand: -25%  
Generic: +29%



**Beta Blockers**  
Brand: +2%  
Generic: +13%



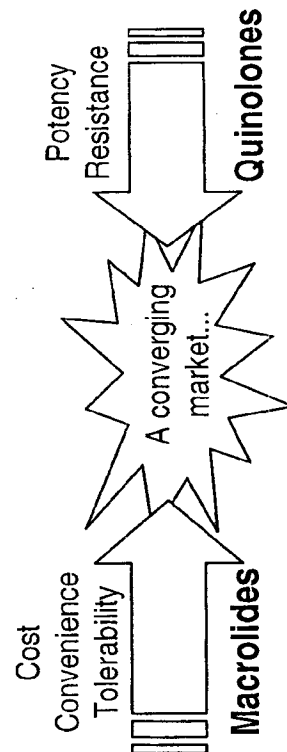
# Antibiotic Classes

3 antibiotic classes dominate the market, representing 89% of global sales

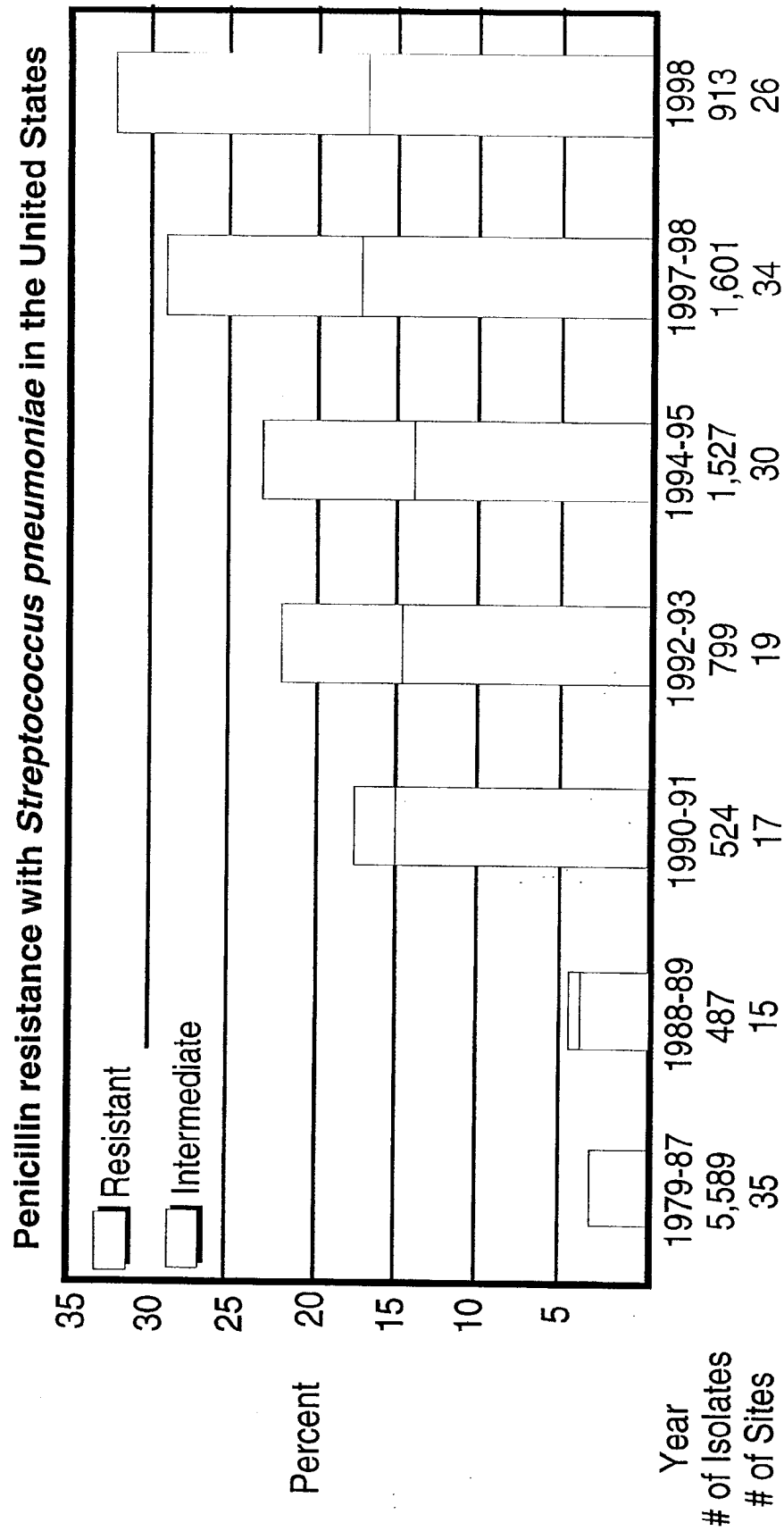
Class Dominant Brand	Other Brands	Global Class Sales (\$MM)	Ped	IV	Comment
B-lactam Augmentin	Ceftin, Cefzil, pens, amox	\$10,561	X	X	<ul style="list-style-type: none"> <li>•B-lactams 1.1% CAGR; -1.4% Y-Y</li> <li>•High generic penetration</li> <li>•Augmentin unique, due to resistance</li> </ul>
Macrolide Zithromax	Biaxin erys	\$4,066	X	X	<ul style="list-style-type: none"> <li>•Macrolides 8.1% CAGR; 2% Y-Y</li> <li>•Zithromax set new standards in cost, convenience, tolerability</li> <li>•Z growth has slowed (5% Y-Y) due to maturing brand and resistance</li> </ul>
Quinolone Levaquin	Cipro Tequin Avelox	\$3,750	Under Dev	X	<ul style="list-style-type: none"> <li>•Quinolones 11% CAGR, 10% Y-Y</li> <li>•Leveraging macrolide resistance to become fastest growing class</li> <li>•New quinolones have overcome narrow spectrum and poor tolerability</li> </ul>

CAGR = Global 1995-2000 compound annual growth rate

- Macrolides expanded the market on the basis of Pen/B-lactamase resistance, cost, convenience, and tolerability
- Quinolones (+11% CAGR) are now driving the market from a macrolide resistance standpoint (while near parity on cost, convenience, tolerability)

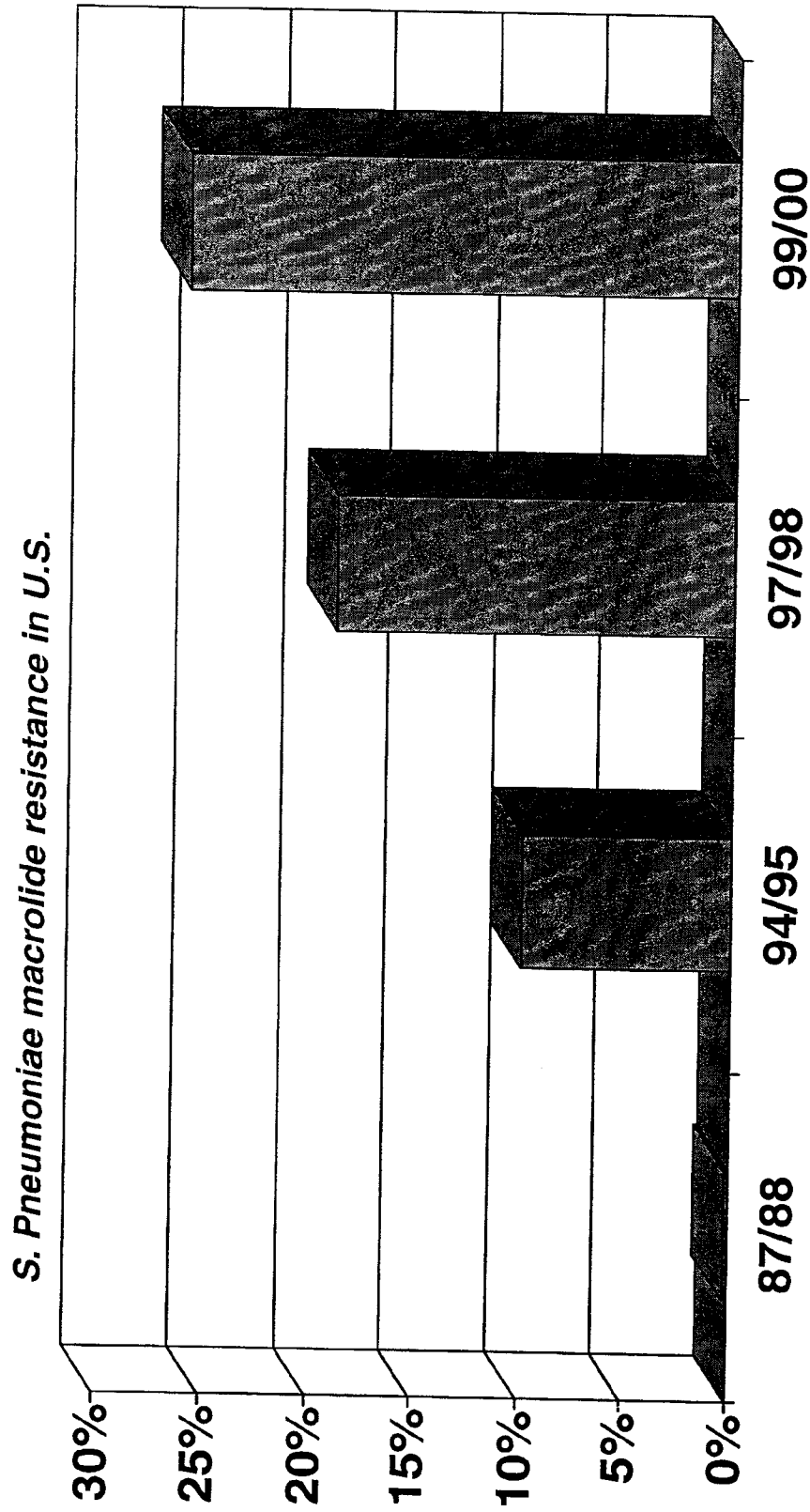


**Biaxin and Zithromax were able to leverage increasing Pen resistance to create a compelling selling proposition**





Quinolones are now leveraging macrolide resistance in the same fashion to become the fastest growing class

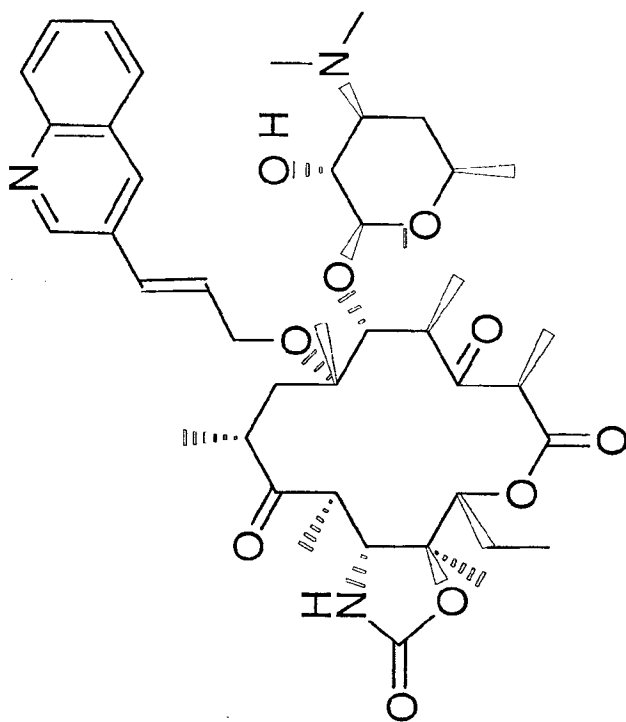


# ABT-773 Target Profile

	ABT-773	Levaquin	Zithromax
Convenience	Target is QD dosing all indications Potential for BID in CAP & sinusitis  Duration: 5d, 10 d (parity to Zithromax) <b>PARITY IF QD</b>	All RTI regimens 500 mg QD, 7-14 d	250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP
Efficacy	Statistically equivalent cure/eradication to comparators; can take advantage of macrolide/penicillin resistance <b>PARITY</b>	Statistically equivalent cure/eradication to comparators; gold standard for CAP with IV; can take advantage of macrolide/penicillin resistance	Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image; subject to increasing levels of macrolide resistance
Activity	Most active agent for Gram + pathogens, including telithromycin; parity for atypicals; parity to Zithromax for Gram -, through inferior to quinolones (weakness)	Highly active against most clinically relevant respiratory pathogens; potential issue with increase in Gram - resistance; theories that Gram + quinolone resistance may increase dramatically/rapidly with increased use	Not as active as clari in Gram + pathogens, increasing macrolide resistance, moderate Gram - activity
Adverse Events	Taste perversion: 4% Diarrhea: 10% <b>COMPARABLE TO BIAXIN XL</b>	Very well tolerated and safe	Very well tolerated; GI disturbance ~ 2-5%; no taste perversion
Resistance Claim	Being pursued; important to development of resistance story; availability of IV will increase likelihood of claim	Claim for pen-R Strep. pneumo	None
Price	Parity to Zithromax	\$60 for 7 days	\$43 for 5 days
Other	Attempt to leverage "best of both worlds" message i.e. potency & resistance coverage of a quinolone with safety & appropriateness of macrolide	Some class-related negative perceptions among some physicians with respect to AEs and appropriate use, but with increased use these barriers are eroding	

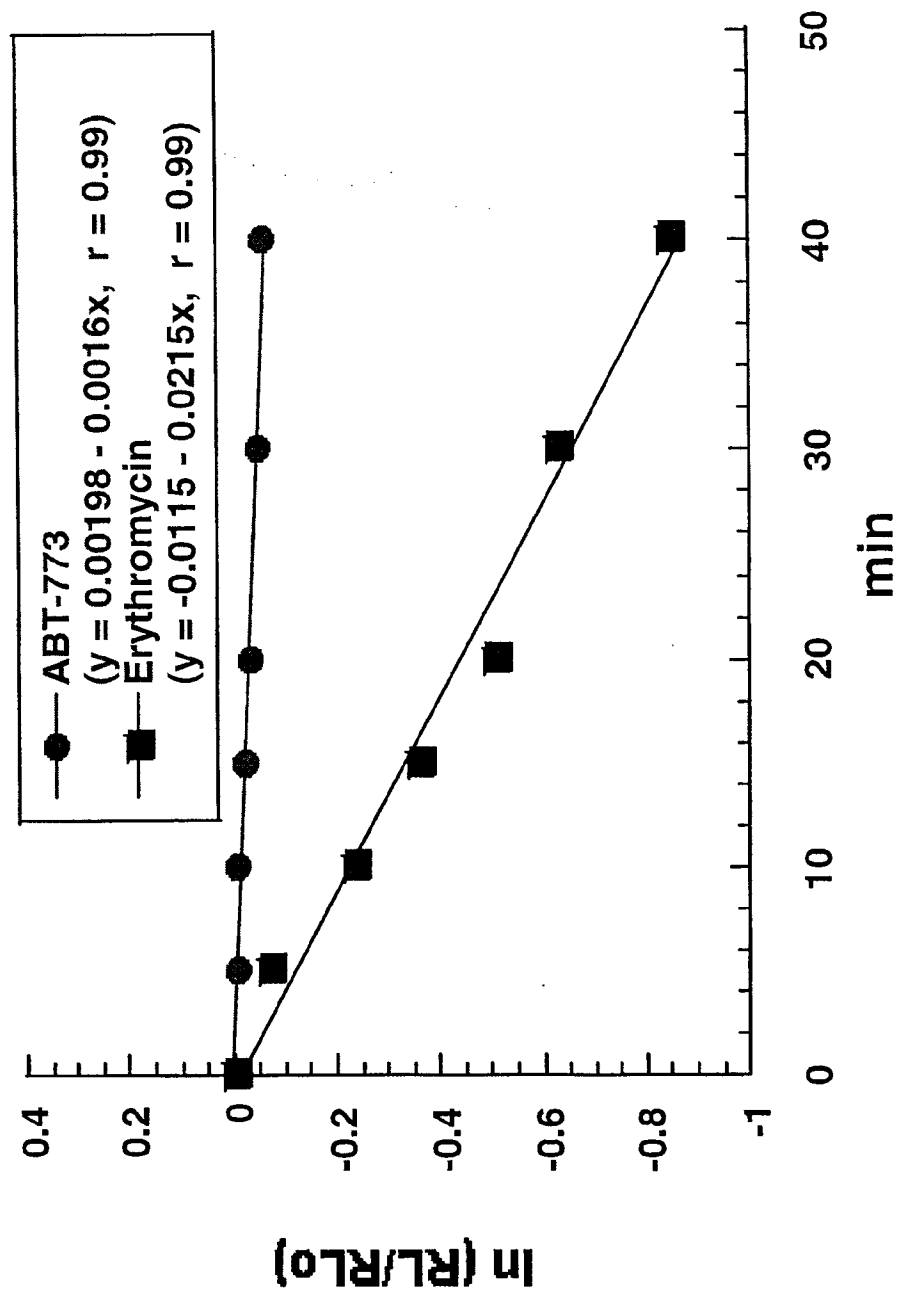
# ABT-773 SAR

- Quinolylallyl propenyl moiety at the 6-0 –position (↑ PK, activity)
- Carbamate group at the 11, 12-position (↑activity vs macrolide-resistant Strep)
- Keto group at the 3-position (confers *erm* non-induction)



- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

# ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.

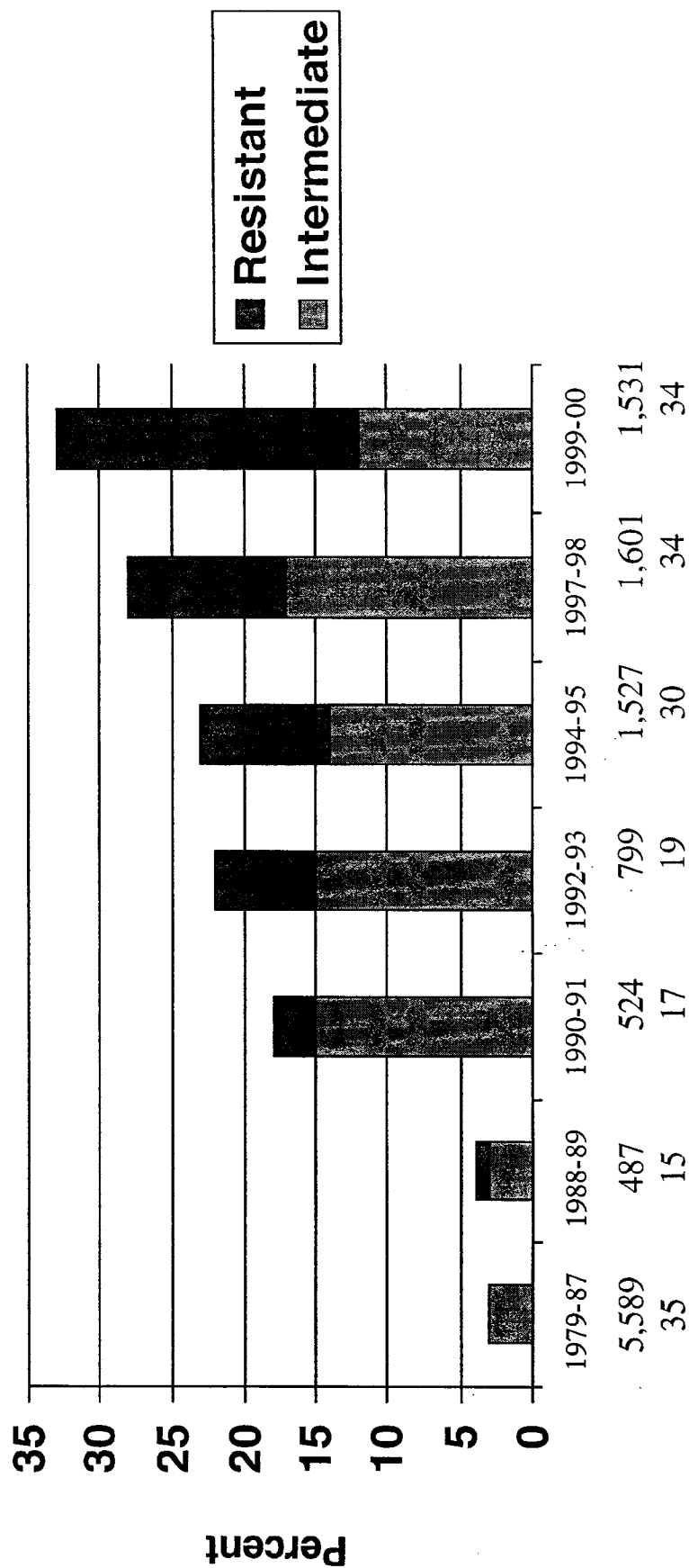
# ABT 773 Microbiology

MIC90	Clari	Trovan*	Ketek	ABT-773
S. Pneumoniae (susc)	< 0.03	0.125	0.008	< 0.002
S. Pneumoniae (mef)	8.0	0.125	1	0.12
S. Pneumoniae (erm)	> 32	0.125	0.12	0.01
S. Pyogenes (mef)	16	0.125	1	0.12
S. Pyogenes (erm)	> 32	0.25	> 8	0.5
M. catarrhalis	0.03	0.015	0.25	0.25
H. influenzae	8	0.015	2	2

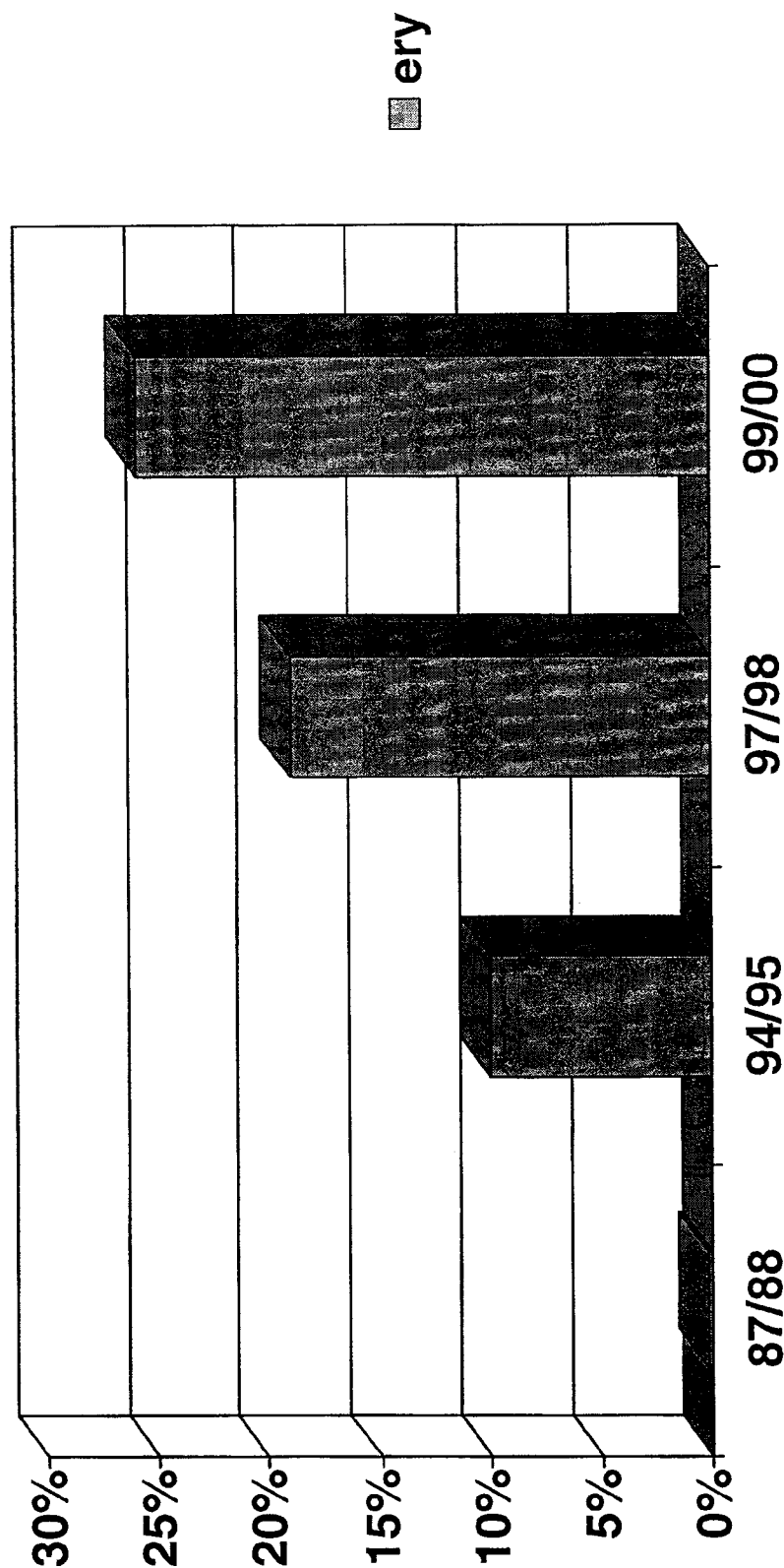
\* Withdrawn from market, but among the more potent quinolones

# Microbiology

## Penicillin resistance with *Streptococcus pneumoniae* in the United States



## *S. pneumoniae* Macrolide Resistance from U.S. Surveillance



US surveillance studies: Doern et al.

# Preclinical/Clinical Issues

- QT prolongation
- Hepatotoxicity



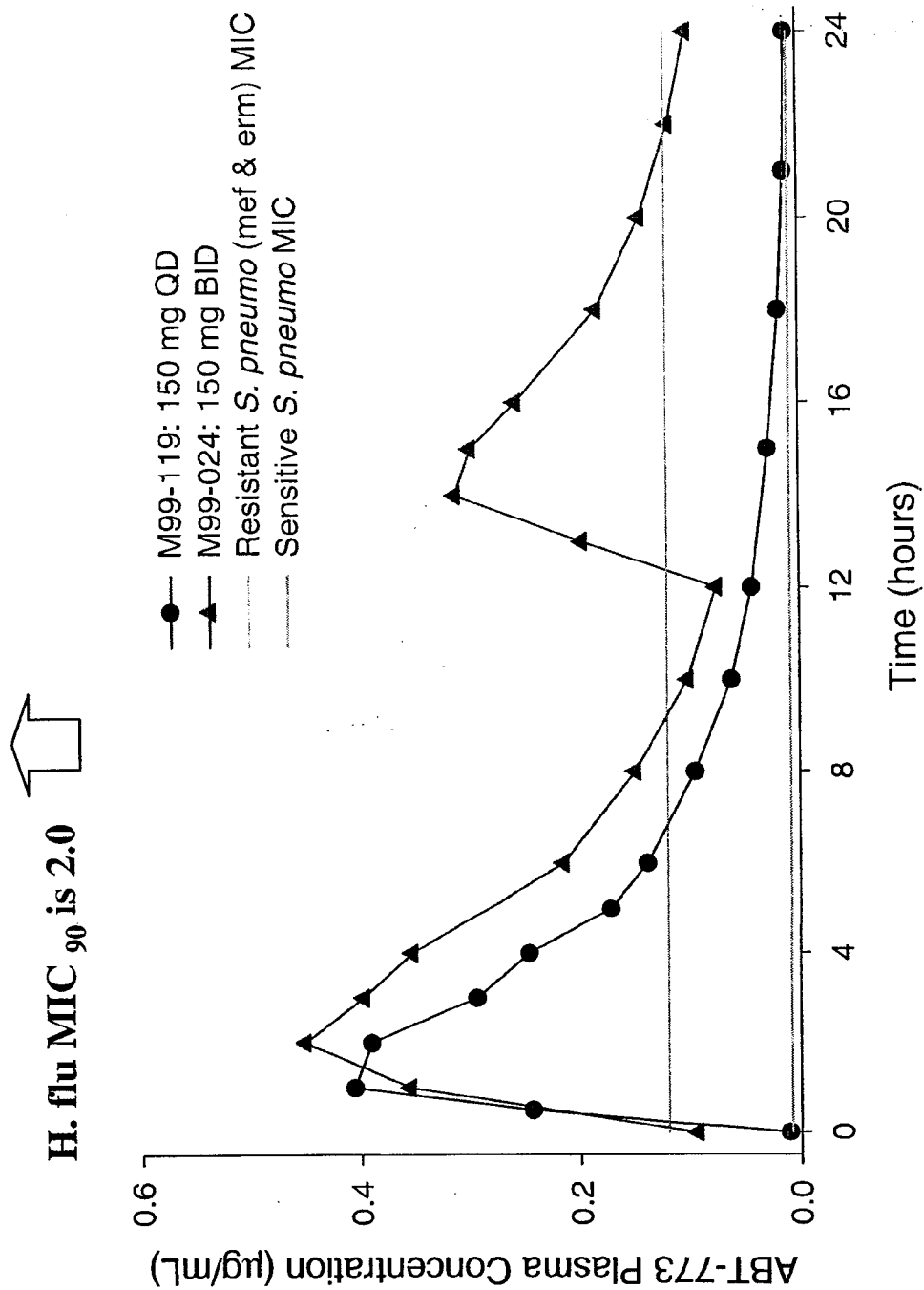
# QT Prolongation

- Purkinje fiber repolarization
  - APD increase at 5 mcg/mL (10x clinical Cmax) in the absence of plasma proteins, but not in their presence
  - Moxi > Clari > Ery ~ ABT-773 > Levo (without plasma)
- Dogs
  - no significant effect on QTc up to 9 mcg/mL
  - 11% increase (40 msec) at 22 mcg/mL
  - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- Humans
  - Possible dose effect in Phase I at daily dose > 800 mg
  - No significant QT effect in ketoconazole interaction study
  - No clinically relevant QT effect in Phase II studies 150 – 600 mg daily (n=412)

# Hepatotoxicity

- Toxicology studies
  - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
  - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
  - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
  - Japanese in bridging study showed increased LFTs.
    - 7 of 42 (17%) Japanese subjects had >3x ULN
    - No evidence of dose response
    - Repeat study in Japan showed no evidence of LFT increases in Japanese (n=60) or Caucasians (n=8).

# ABT 773 Pharmacokinetics



# Phase II Clinical Studies

Study	Dose/Duration	Number of subjects
ABECB	150, 300 or 600 mg OD Duration: 5 days	N = 384
Acute Sinusitis	150, 300, or 600 mg OD Duration: 10 days	N = 292
CAP	300 or 600 mg OD Duration: 7 days	N = 187

# Phase II Results

## Combined ABECB, CAP, ABS Clinical Response

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

# ABT 773 Phase II Findings

## Combined ABECB, CAP, ABS Adverse Events

	<u>150 mg QD</u>	<u>300 mg QD</u>	<u>600 mg QD</u>
<b>GI and Taste</b>			
<b>Taste Perversion</b>	4% (8/223)	17% (55/322)	27% (87/318)
<b>Diarrhea</b>	10% (22/223)	11% (34/322)	19% (60/318)
<b>Nausea</b>	5% (12/223)	12% (40/322)	26% (83/318)
<b>Vomiting</b>	2% (4/223)	6% (19/322)	14% (44/318)

# Phase II: 150 mg QD vs 300 mg QD

Phase IIb Data: Intent-to-treat									
		Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD	85%	104/123			82%	72/88	83%	176/211
		83%	107/129	84%	80/95	80%	72/90	82%	159/314
	Bacteriological Cure	<i>H. flu</i>	89%	17/19			60%	3/5	83%
81%			17/21	100%	9/9	100%	7/7	89%	33/37
<i>S. pneumo</i>		77%	10/13			100%	3/3	81%	13/16
		90%	9/10	82%	14/17	100%	8/8	89%	31/35

# Community-Acquired Pneumonia

## Clinical Response

	300 mg	600 mg
--	--------	--------

Clin and Bact. Eval	92% (54/59)	82% (47/57)
---------------------	-------------	-------------

Clin Eval	92% (72/78)	80% (56/70)
-----------	-------------	-------------

ITT	84% (80/95)	73% (65/89)
-----	-------------	-------------



# Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD selected for ABECB and pharyngitis in pivotal phase III comparative studies
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

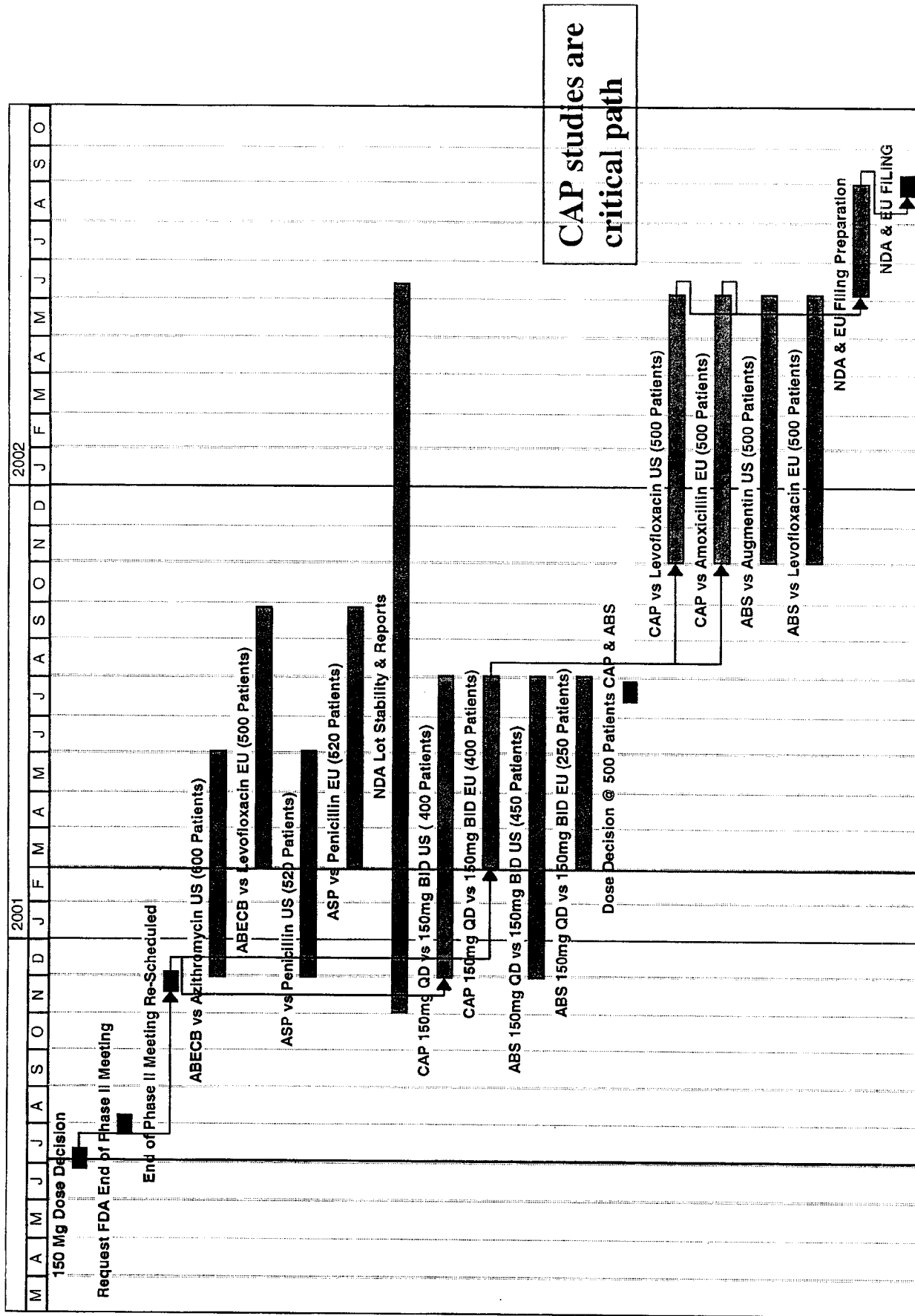
## Dose selection: Divergent U.S. and European regulatory and commercial considerations

- **US**
  - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
  - Approval on indication-by-indication basis
- **Europe**
  - Relatively minor commercial impact of BID dosing
  - CAP indication is critical for overall approval

# ABT 773 Indications

<b>Infection</b>	<b>Dosage</b>	<b>Duration</b>
Pharyngitis/Tonsillitis (ASP)	150 mg QD	5 d
Acute bacterial exacerbation of chronic bronchitis (ABECB)	150 mg QD	5 d
Acute bacterial sinusitis (ABS)	150 mg QD or BID	10 d
Community-acquired pneumonia (CAP)	150 mg QD or BID	10 d

# ABT 773 Development Timeline



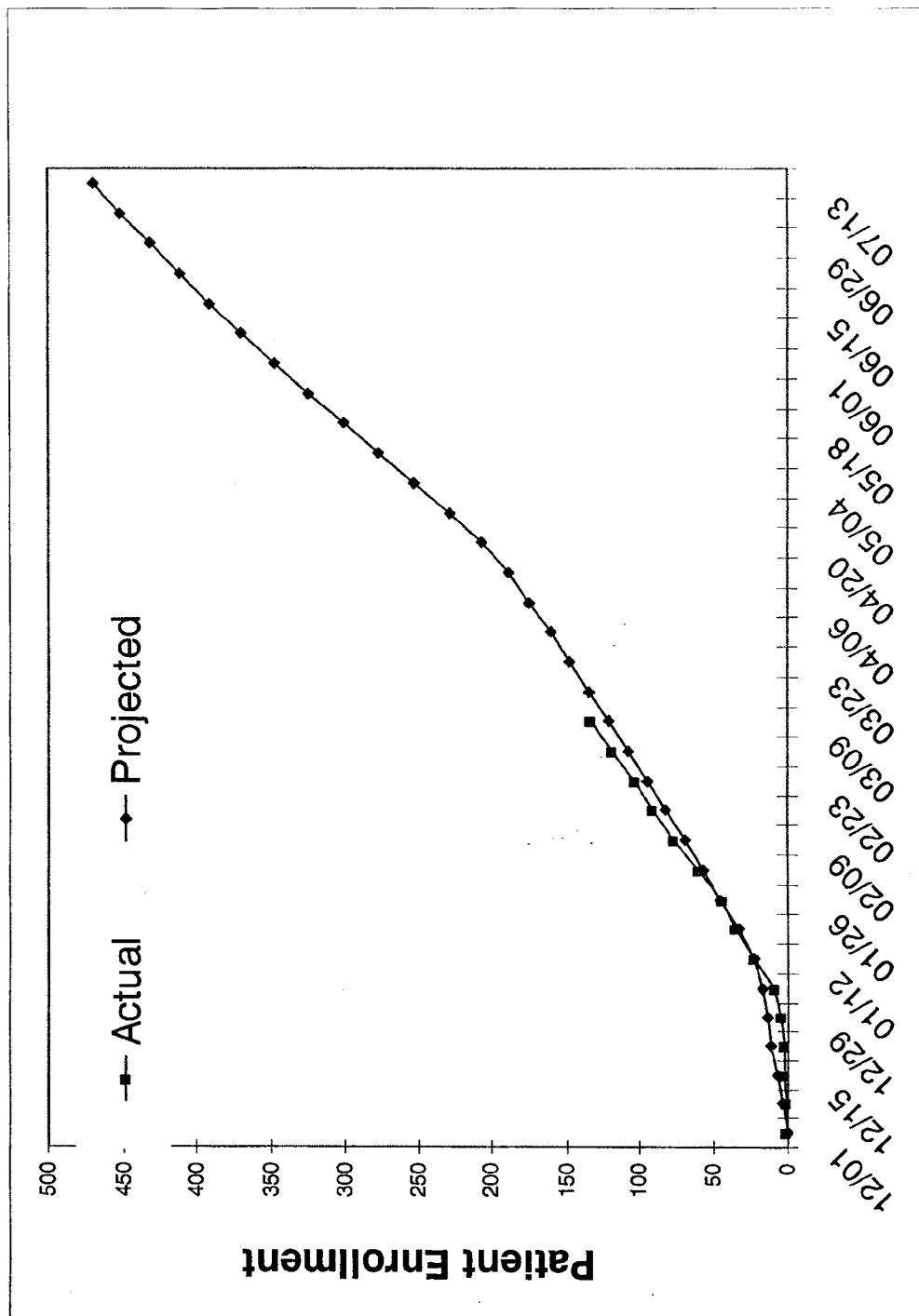
## Phase III: ABECB and ASP

Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-216 ABECB vs Azithromycin	600	Nov. 2000	US	277	110
M00-217 ABECB vs Levofloxacin	500	Jan. 2001	EU	2	100
M00-222 ASP vs Penicillin	520	Jan. 2001	EU	1	45
M00-223 ASP vs Penicillin	520	Nov. 2000	US	337	45

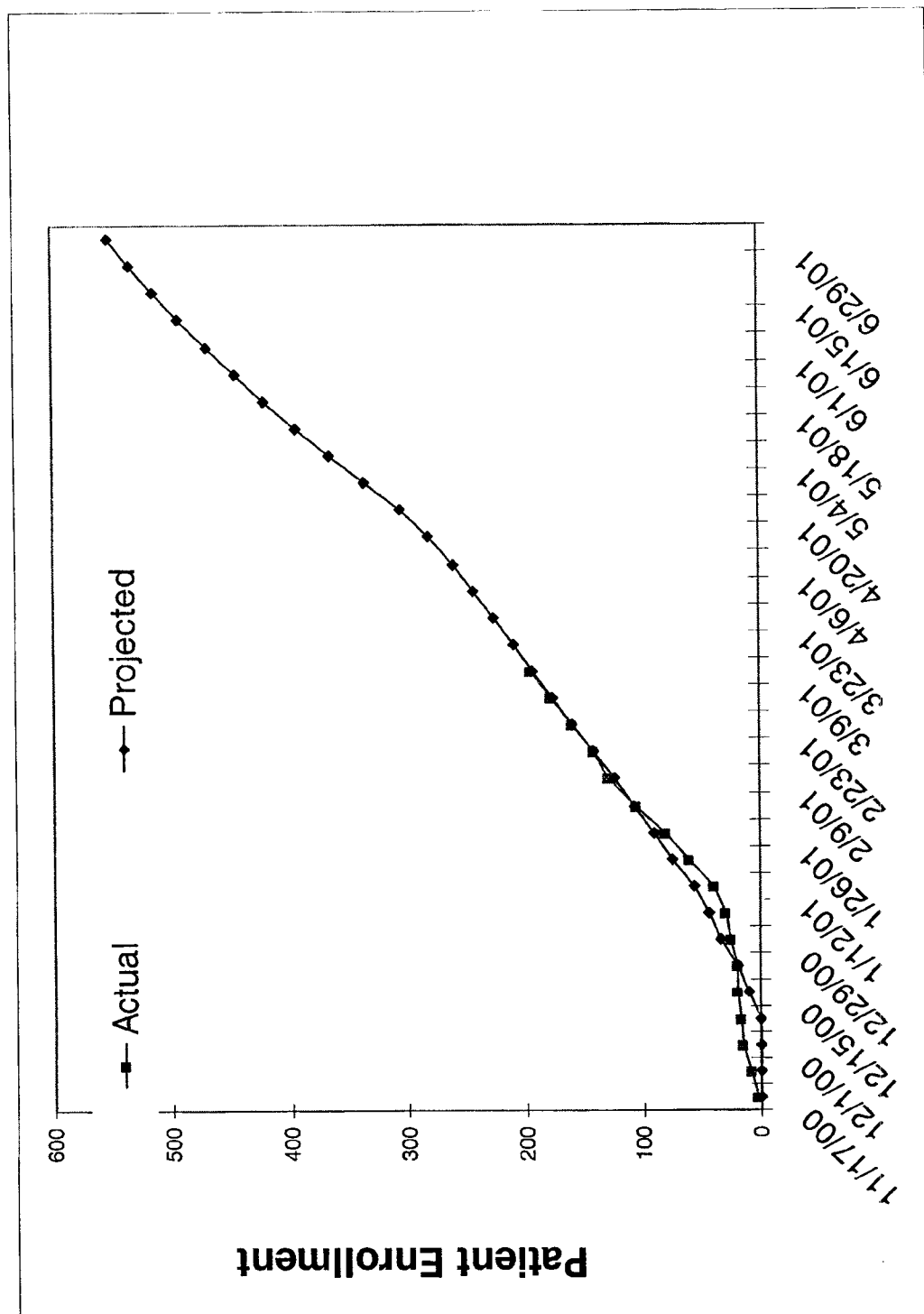
# Phase III: CAP and ABS

Study	Target Enrollment	Start Date	Location	Enroll Status	# sites
M00-219 CAP 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	143	294
M00-221 CAP vs Levofloxacin	500	Nov. 2001	US		200
M00-220 CAP vs Amoxicillin	500	Nov. 2001	EU		200
M00-225 ABS 150mg QD vs BID	500 for dose selection	Nov. 2000	US, EU	205	114
M00-218 ABS vs Augmentin	500	Nov. 2001	US		90
M00-226 ABS vs Levofloxacin	500	Nov. 2001	EU		90

# CAP dose-ranging study: enrollment status



# Sinusitis dose-ranging study: enrollment status





# Progress towards resistance claim

Pathogen	M00-216 ABECB	M00-219 CAP	M00-225 ABS
Subjects with Positive culture	266	60	77
<i>S. Pneumoniae</i> isolates	16	16	19
Resistant <i>S.pneumo</i>	7	9	7
<i>Penicillin</i> resist	0	1	1
<i>Macrolide</i> resist	2	0	3
<i>PRSP &amp; MRSP</i>	5	8	3
# of isolates proposed for resistance claim			
PRSP	15	15	15
MRSP	15	15	15

# ABT 773 Contingency Plan

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
- Dose decision delayed to Sept 2001, filing delayed
- Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere

# 2001 Clinical Budget (\$MM)

• 2001 Clinical Program	61.7
• Assumptions to achieve budget	
• Complete 2000/01 Phase III Studies by June 2001 in U.S. and Europe	
• Initiate 2001/02 Phase III Studies by Nov. 2001	
• Conduct start up activities <b>only</b> in Southern Hemisphere, <b>do not</b> initiate enrollment	
• Contingency costs	2.0
• Assumptions	
• Continue European ABECB and ASP studies to Dec 2001	
• Enroll CAP and ABS studies in the Southern Hemisphere through Sept. 2001	
• Partial cost offset due to lower enrollment in U.S. and Europe	

# Other Filing Options

*Other filing options have been evaluated and are less desirable (regulatory, commercial, logistic)*

Option	Indications	Dose	Filing Date US	Filing Date Europe
Option 1 File without CAP indication in the U.S., delay Europe filing	ABECB/ASP/ABS	150mg QD	Aug 2002	June 2003
	CAP	150mg QD or BID	Aug 2003	June 2003
Option 2 Make BID dose decision for CAP and ABS now.	ABECB/ASP	150mg QD	Aug 2002	Aug 2002
	CAP/ABS	150mg BID	Aug 2002	Aug 2002
Option 3 Delay Dose Decision to Phase III	ABECB/ASP/ABS 3 arm CAP Study	150mg QD or BID	Dec 2002	Dec 2002
Option 4 Run separate US and European clinical programs	ABECB/ASP	150mg QD	Dec 2002	Aug 2003
	CAP/ABS	150mg QD US 150mg BID Europe	Dec 2002	Aug 2003

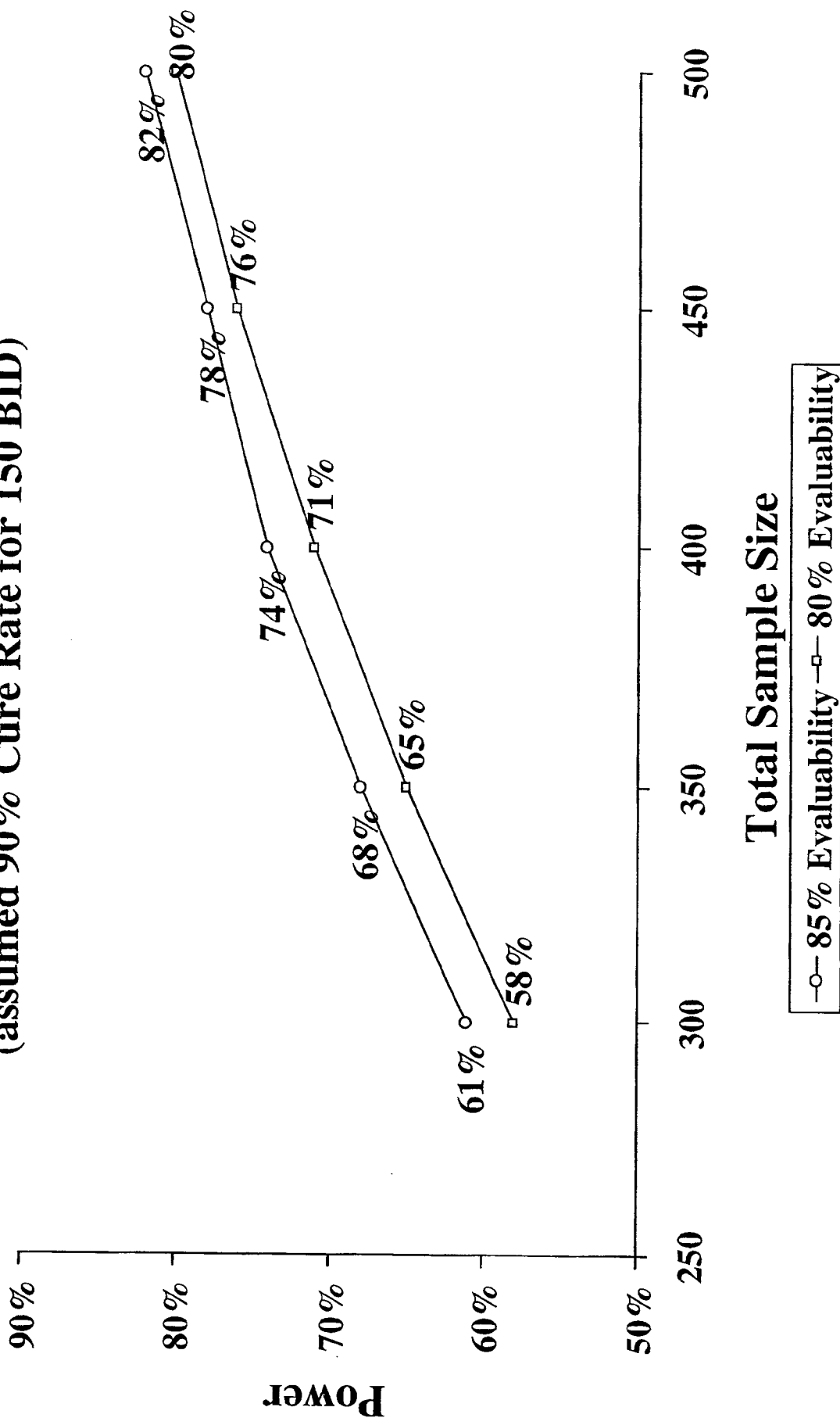
# Possibilities

- Make enrollment targets on time
- A little behind
- Way behind

# Activities-to-date to address CAP enrollment

- Increased European sites from 79 to 130 in Nov. 2000
- Site approvals expedited
  - Amendments translated and submitted to Ethics Committees for 350 sites in 1 month
  - CRO actively encouraging investigators to expedite EC approval process as much as possible
- Increased investigator fees
- Increased site follow up/communication
- Diligent CRO management

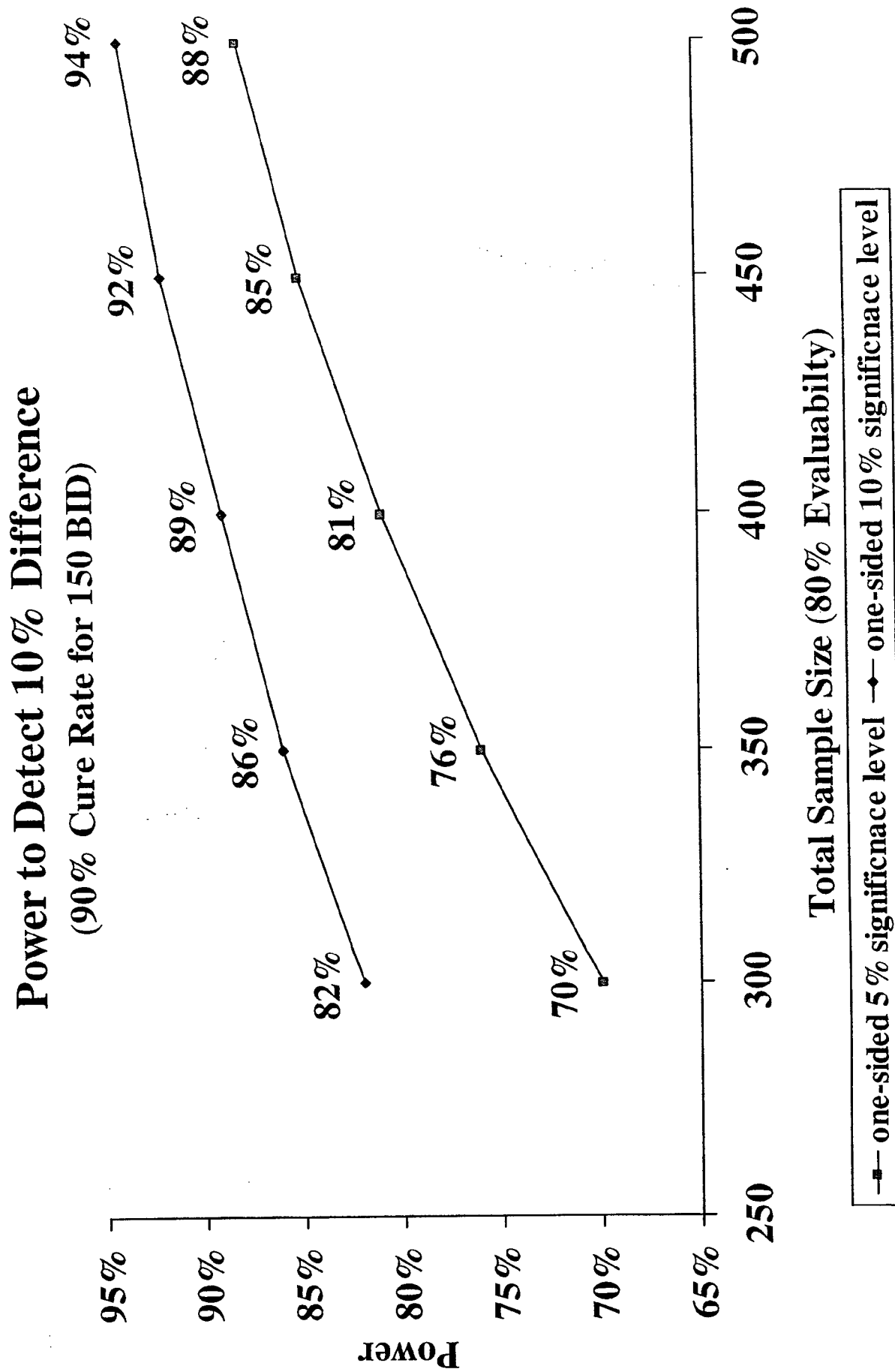
# **Power to Detect 10% Difference** (assumed 90% Cure Rate for 150 BID)



**Statistical power is a  
function of:**

- Sample size
- Treatment arm differences
- Level of statistical significance





# Possible outcomes of dose-ranging studies

**QD is:**

CAP	Sinusitis	Decision
Worse	Worse	BID
Same	Worse	BID
Worse	Same	BID or BID/QD
Same	Same	QD

# Agenda

- Market and trends
- Molecule
- Microbiology
- Pharm/tox
  - QT prolongation
  - Hepatotoxicity
- Clinical development
  - Phase I/II summary
  - Dose selection
  - Phase III program
  - Contingency plans
- Timeline and budget
- IV formulation
- Summary of key issues and action plans

# ABT-773 IV Formulation

## Strategic, Commercial, and Technical Value

- **Strategic Value**
  - IV represents a channel not currently served by Anti-infective Franchise
  - Leverages presence of MCRs and experience with ID community
- **Commercial Value**
  - IV availability improves formulary access to molecule
    - Potential advantage over telithromycin, which will not have an IV
    - Would be competitive with Zithromax, Tequin, Avelox which have IV
  - Positive impact on tablet formulation
    - estimated \$36MM incremental to peak tablet sales due to step-down therapy
    - Enhances overall “potency” image of brand
- **Technical Value**
  - Support for *S. pneumoniae* Resistance claim
    - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
  - Provides additional information on QT effects

# **ABT-773 IV**

## **Planned Clinical Program**

- |  |        |
|--|--------|
| • Single Dose-rising Phase I study         | May/01 |
| • Multiple Dose Phase I with selected dose | Aug/01 |
| • File US IND                              | Nov/01 |
| • Initiate Phase III                       | Jan/02 |
| – 2 step-down CAP studies (US/Europe)      |        |
| – 2-3 days dosing                          |        |
| – Two seasons to complete                  |        |
| • Filing                                   | Dec/03 |

- |   |
|---|
| <ul style="list-style-type: none"><li>• IV launch currently lags tablet launch by 1 year</li><li>• further delays will reduce the potential value</li></ul> |
|---|

## IV Development Cost

	Thru 2000	2001	2002	2003 to NDA	Total
Clinical Program	0.2	4.0	6.0	2.5	12.7
Phase I Single Rising Dose		0.5			0.5
Phase I Multiple Dose		0.4			0.4
Phase III 2 step-down CAP Studies (US/Europe)		2.9	6.0	2.5	11.4
CMC	1.0	2.5	1.8	1.3	6.6
Drug Safety/Other	1.0	1.0	1.0	1.0	4.0
Total by Year	2.2	7.5	8.8	4.8	23.3

# Summary: Key Issues

- **QT Prolongation**
  - Possible class labeling, with resulting safety perception
- **Resistance claim**
  - Key differentiating feature
  - Bacteremic isolates requested by FDA requires IV
- **IV Formulation**
  - Strengthens strategic, commercial, and technical value of product
- **QD vs BID dosing**
  - Divergence regulatory and commercial considerations in US vs Europe
- **Delayed Phase III program**
  - Delayed dose selection decision beyond July/Aug 2001 could delay filing

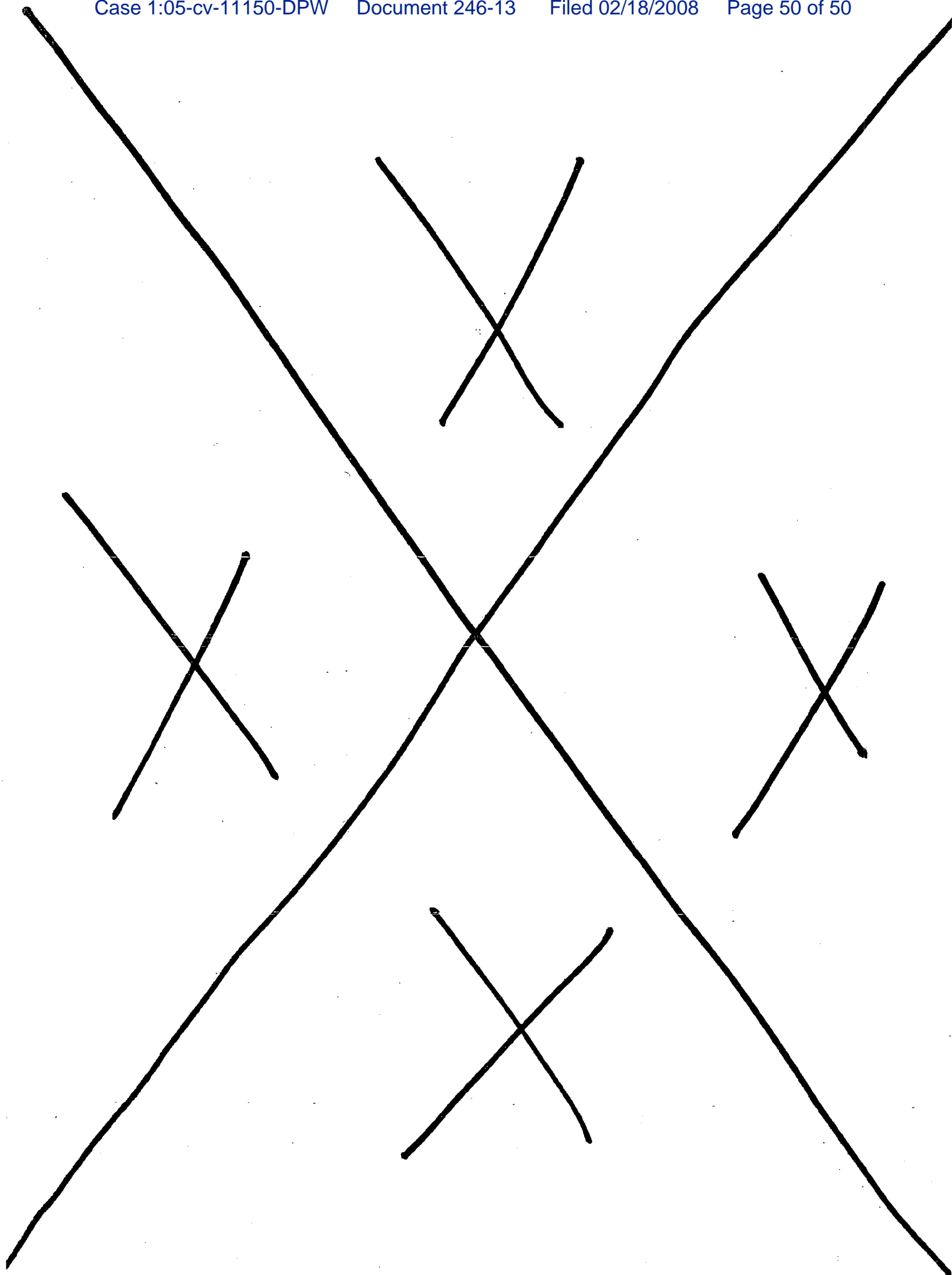
# ABT-773 Action Plans

Key Issue	Action Plans
<b>QT Prolongation</b>	<ul style="list-style-type: none"> <li>▪ Conduct EKG monitoring in Phase III to gather additional data on QT prolongation</li> <li>▪ Anticipate and fulfill regulatory expectations for animal and human data</li> </ul>
<b>Resistance claim</b>	<ul style="list-style-type: none"> <li>▪ Accrue sufficient patients to obtain necessary organisms</li> <li>▪ IV formulation would access bacteremic patients</li> </ul>
<b>IV Formulation</b>	<ul style="list-style-type: none"> <li>▪ Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding</li> </ul>



# ABT-773 Action Plans

Key Issue	Action Plans
QD vs BID dosing	<ul style="list-style-type: none"><li>▪ Select dose based on outcome of current QD vs BID trials</li><li>▪ Minimize regulatory risk</li><li>▪ Optimize global commercial opportunity</li></ul>
Delayed Phase III program	<ul style="list-style-type: none"><li>▪ CAP Study sites increased in the US and Europe from 209 to 300 sites</li><li>▪ Southern hemisphere contingency</li><li>▪ Re-evaluate other contingency plans</li></ul>





# **Project Review**

## **ABT-089 and ABT-594**

**February 2, 2001**

# Project Review

- ABT-089

REDACTED

- ABT-594

- Overview, upcoming milestone: June 2001
- Follow-on strategy

# Neuronal Nicotinic Receptor (NNR) Program

- Scientific leadership position for Abbott
- An emerging diversity of receptors
- Multiple potential therapeutic targets

**ABT-089**

**REDACTED**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002317**

**ABT-089**

**REDACTED**

**HIGHLY**

**CONFIDENTIAL**

**ABBT 0002318**



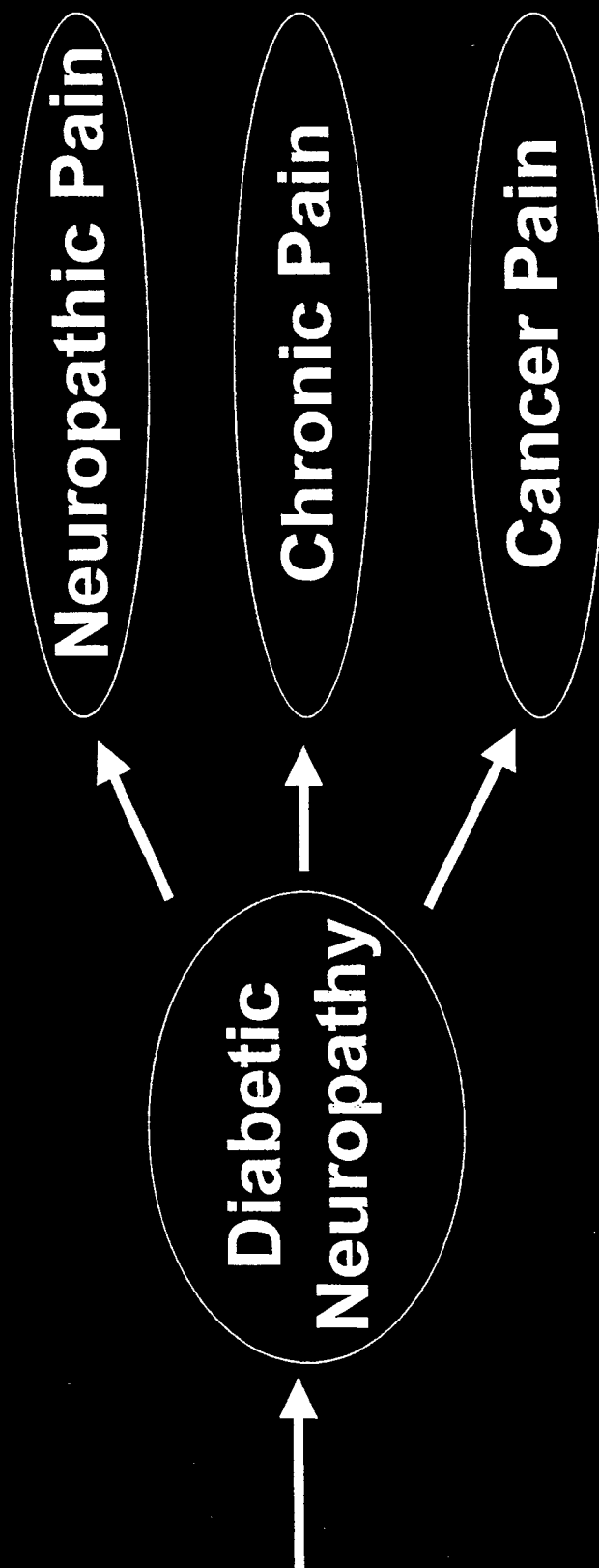
# ABT-594

## *Overview*

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

# ABT-594

*Therapeutic Utility*



**REDACTED**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002321**

REDACTED

HIGHLY

ABBT 0002322

REDACTED

**REDACTED**

REDACTED

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**ABBT 0002326**

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**ABBT 000232R**



REDACTED

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**ABBT 0002330**

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ABBT 0002331

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ARBT 0002355

REDACTED

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CONFIDENTIAL

ABBT 0002356

**REDACTED**

REDACTED



# **ABT-594 Project Review February 2, 2001**

## **Introduction**

**Chris Silber**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002369**

# ABT-594 Project Review

## *Agenda*

- |                           |                  |
|---------------------------|------------------|
| • Introduction            | Chris Silber     |
| • Pharmacological Profile | Jim Sullivan     |
| • Clinical Overview       | Bruce McCarthy   |
| • Commercial Assessment   | Andrea Landsberg |
| • Go/No Go Process        | Bruce McCarthy   |
| • Follow-On Strategy      | Mike Meyer       |

# ABT-594

## *Overview*

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- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

## Pain Prevalence

- 22% primary care patients worldwide have persistent pain
- Neuropathic pain
  - 20% of diabetics
  - 40% of HIV infected
  - 36% of cancer patients

# Pain Therapeutics Market

- \$12 billion in sales of key classes (NSAIDs, COX-2s, opioids, non-opioids)
- \$700 million in sales of key neuropathic pain compounds
  - use largely off-label
  - low cost generics

# Neuropathic Pain

## *Treatment*

### Some efficacy

(at best 40% vs. 20% placebo)

- Tricyclic antidepressants
  - Amitriptyline, desipramine, etc.
- Anti-epileptic drugs
  - Carbamazepine
  - Gabapentin (Pregabalin)
  - Topiramate, others
- Sodium channel blockers
  - Lidocaine
- Opioids
  - Tramadol

### No efficacy

- SSRIs
- NSAIDs/COX-2

# **Broad-Spectrum, Non-Opioid Analgesic Activity by Selective Modulation of Neuronal Nicotinic Acetylcholine Receptors**

A.W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon,  
D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz,  
A. H. Dickenson, R. D. Porsolt, M. Williams, S. P. Arneric

SCIENCE • VOL. 279 • 2 JANUARY 1998

# Development Strategy

## Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic surgery  
Dysmennorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

## Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

## Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TMJ disorder  
Bursitis  
Tendinitis  
Chronic visceral pain



# Development Strategy

## *Choose Portals of Entry*

**Molar**

**→ Acute Pain**

**Extraction**

**Peripheral**

**→ Neuropathic Pain**

**Neuropathy**

**Osteoarthritis**

**→ Chronic Nociceptive  
Pain**

# ABT-594

## *Current Label Target*

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

### Upside Claim

- Neuropathic Pain
- Post herpetic neuralgia
- OA Pain
- Chronic Pain
- Cancer Pain

### General Pain Claim

- Not viable due to 1.5 hour onset

# ABT-594

## *Go/No Go Process*

- Decision analysis (DSG) will be used as a tool to determine milestone criteria
  - Efficacy and safety
  - Titration effects
  - Dose selection
  - Indications
  - Market research

# ABT-594

## *Phase III Clinical Plan*

	U.S.	Europe	Japan
Diabetic neuropathy	2 (n=1200)	2 (n=1200)	1 (n=300)
Long-term safety	1 (n=500)	1 (n=500)	-
Gabapentin comparator	-	1 (n=320)	-
Other neuropathic pain (Phase 3B) post herpetic neuralgia, sciatica	2 (n=600)	-	-

	<u>01</u>	<u>02</u>	<u>03</u>	<u>Total</u>
Cost (\$ million)	6.1	59.6	55.7	121.4

# ABT-594

## *Phase 2 to 3 Transition*

Milestone review	6/01
End of Phase 2 package/request	9/01
Start manufacture Phase 3 supplies	9/01
Ship first Phase 3 supplies	2/02
Initiate Phase 3	3/02
Regulatory filings	9/03

# ABT-594

## *Overview*

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# **ABT-594 Project Review February 2, 2001**

## **Pharmacological Profile**

**Jim Sullivan**

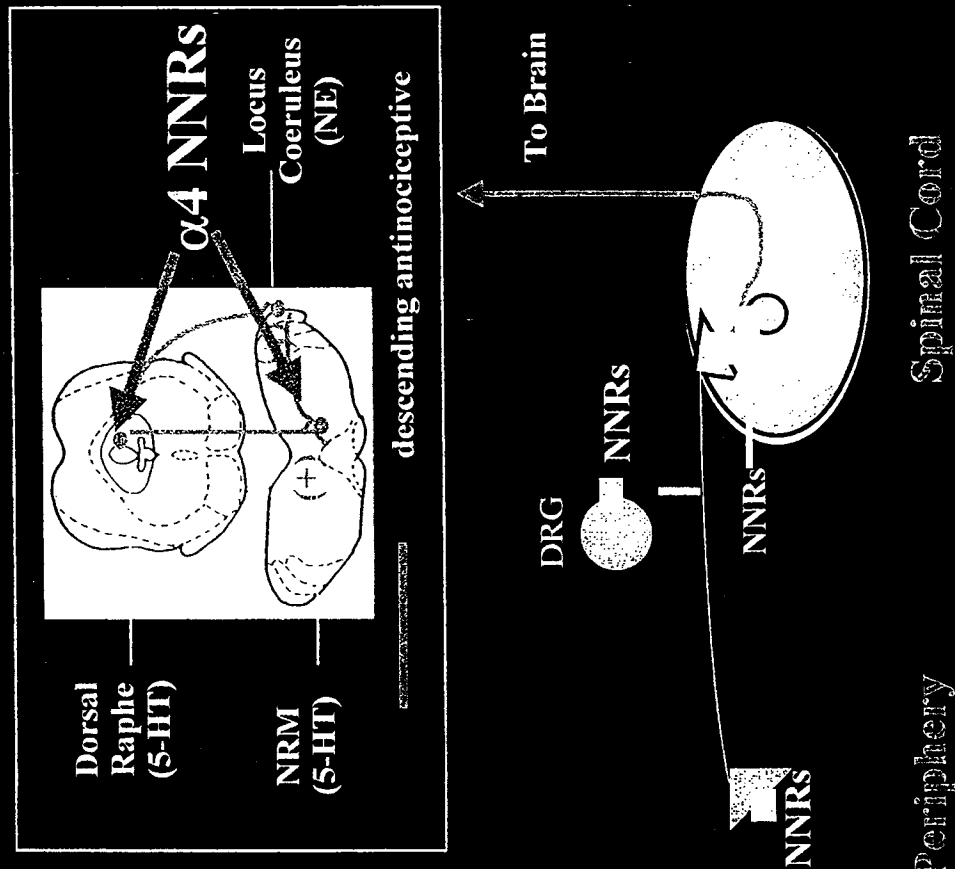
# ABT-594: Preclinical Pharmacology

- Rationale for NNRs and pain
  - Knockout, antisense and pharmacological validation
- *in vitro* and *in vivo* profile of ABT-594
  - Efficacy
  - Safety



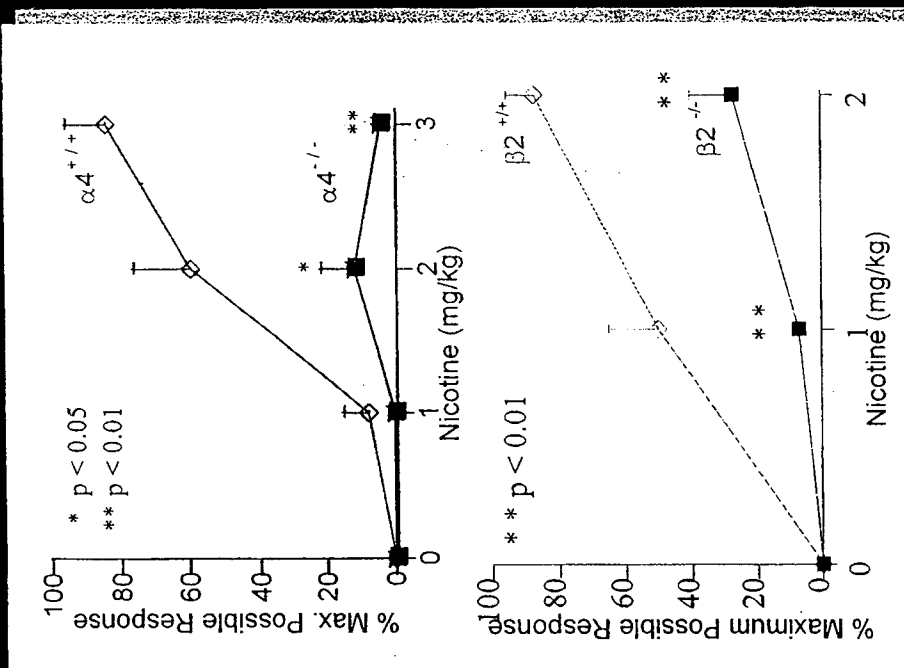
# NNRs and Pain: NNRs are Expressed in Pain Pathways

- CNS
  - $\alpha 4$  NNRs are localized in NRM and dorsal raphe (Key CNS pain center)
- Spinal Cord
  - NNRs are expressed in dorsal horn neurons (key spinal cord pain processing center)
- Sensory Neurons
  - $\alpha 4\beta 2$ ,  $\alpha 3\beta 4$ ,  $\alpha 7$  NNRs are expressed in DRG and on central and peripheral C-fiber nociceptors



# NNRs for Pain: Role of $\alpha 4$ and $\beta 2$ NNRs Established Using Knockout Mice

- In either  $\alpha 4^{-/-}$  or  $\beta 2^{-/-}$  mice, neither nicotine nor epibatidine was active in the hot plate assay (supraspinal mechanism)

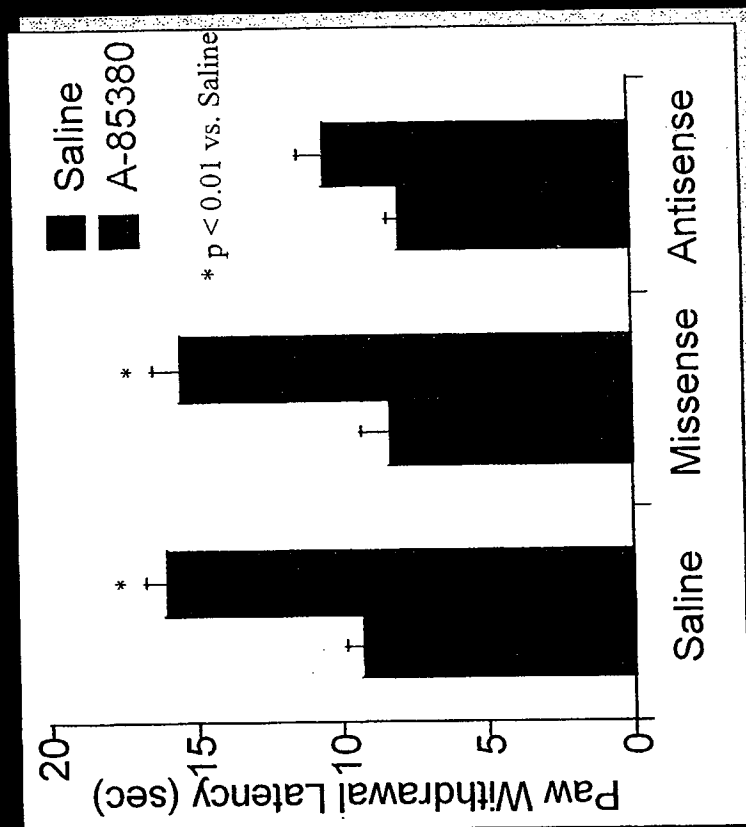


Marubio, et al. *Nature* 1999 398, 805-810.

# NNRS for Pain: Target Validation Using $\alpha 4$ Antisense

## *$\alpha 4$ Antisense Treatment Attenuates Antinociception in the Hot Box Model of Acute Thermal Pain*

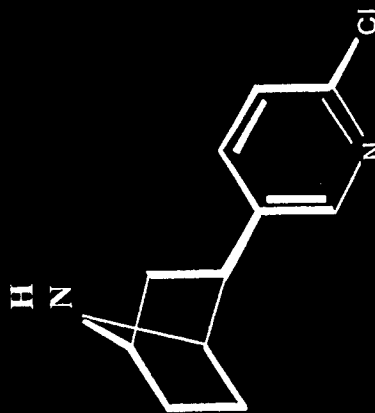
- Rats received either a saline, missense, or antisense continuous i.c.v. infusion (0.75 nmol/hr) for 7 days
- Rats were evaluated in a crossover design in the hot box model of acute thermal pain



Bitner, et. al, *Brain Res.* 871: 66, 2000

# Target Validation: NNR Agonists Are Analgesic

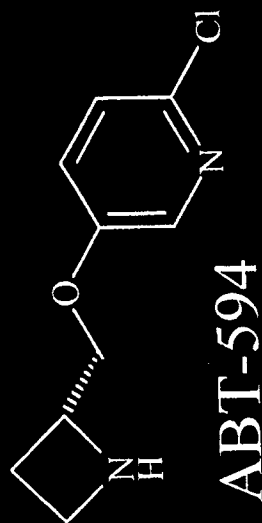
- NNR agonists are -
  - Antinociceptive (capable of raising nociceptive thresholds in naïve animals)
  - Antihyperalgesic (capable of reversing the reduction in nociceptive thresholds following injury)
- Epibatidine (key discovery)
  - 200x more potent than morphine
  - Non-opioid
  - Potent NNR agonist
  - BUT highly toxic



Radio and Daly, *Mol. Pharmacol.*  
45: 563, 1994.

# NNRs and Pain: ABT-594

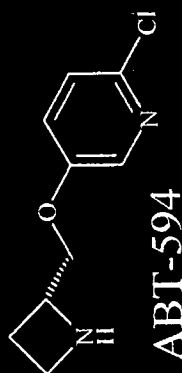
## *Goal*



- Maintain broad spectrum analgesic efficacy of epibatidine
  - Maintain potency at  $\alpha 4$  containing NNRs
- Decrease side-effect liabilities by decreasing activity at
  - Neuromuscular junction nicotinic receptors ( $\alpha 1\beta\delta\gamma$ )
  - Ganglionic NNR subtypes ( $\alpha 3\beta 4$ ,  $\alpha 3\alpha 5\beta 2\beta 4$ )

# ABT-594 is a More Selective NNR than Epibatidine in Radioligand Binding Studies

Binding Site (Ki; nM)	Epibatidine	ABT-594
Cytisine Binding Site ( $\alpha 4\beta 2$ )	0.042	0.037
BTX Binding Site (Peripheral) ( $\alpha 1$ )	2.4	16,600

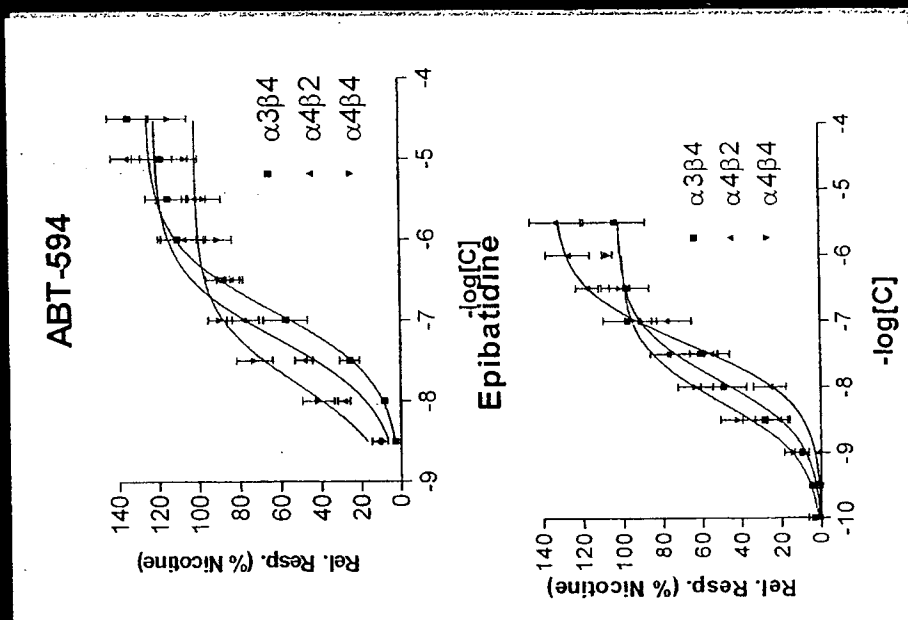


- ABT-594 retains potency of epibatidine at the  $\alpha 4\beta 2$  binding site
- ABT-594 is > 5000-fold less potent than epibatidine at the peripheral neuromuscular junction nicotinic receptor

# In Vitro Functional Profiles of ABT-594 and Epibatidine

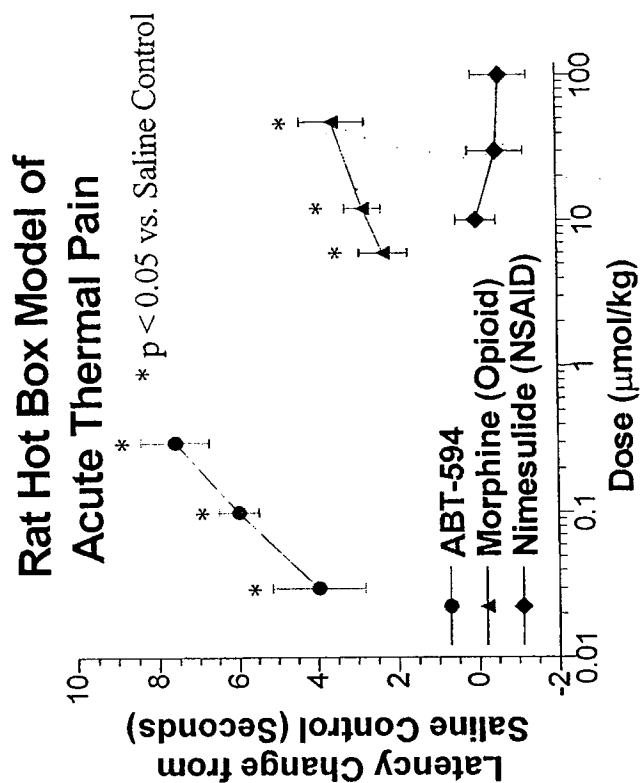
## Functional Activity

- Rank order of potency
  - ABT-594:  $\alpha 4\beta 4 \sim \alpha 4\beta 2 > \alpha 3\beta 4$
  - Epibatidine:  $\alpha 4\beta 4 \sim \alpha 3\beta 4 \sim \alpha 4\beta 2$
- ABT-594 displays modest  $\alpha 4$  vs  $\alpha 3\beta 4$  selectivity
  - Compounds with greatly improved selectivity have been identified



# ABT-594: In Vivo Efficacy in Models of Acute Thermal Pain

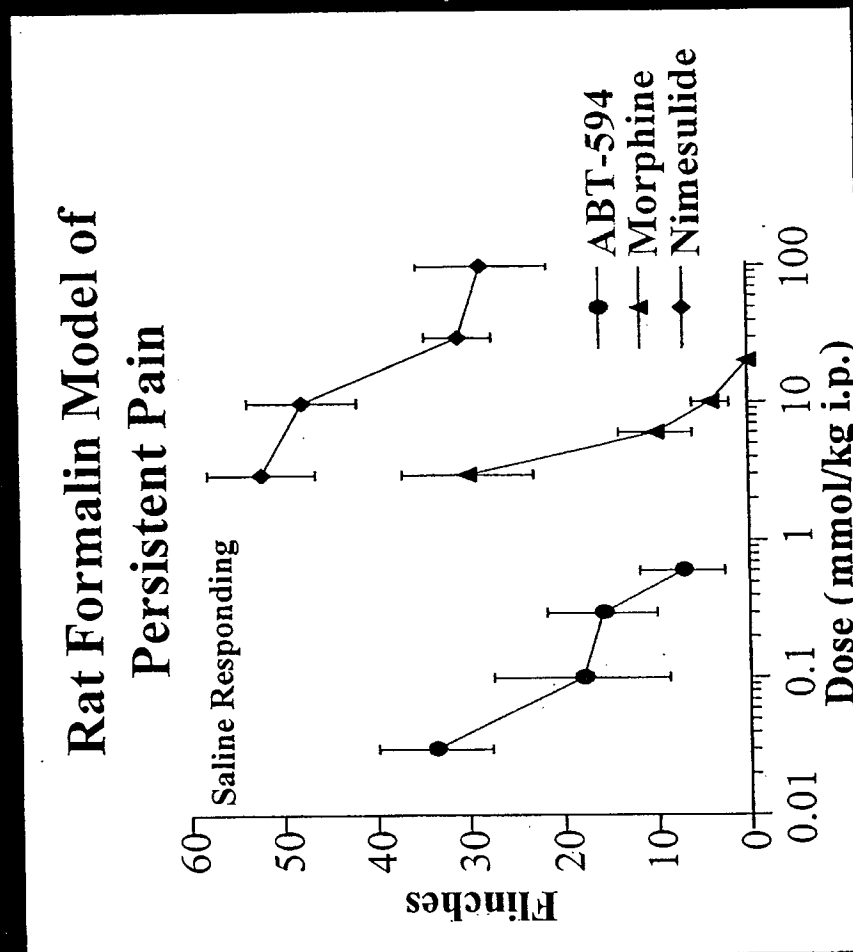
- ABT-594 is potent and efficacious in the Hargreaves Hot Box model of thermal nociception
- Onset of Efficacy = < 30 min
- Duration of efficacy ~ 2 hrs
- The effects of ABT-594 are blocked by the nicotinic antagonist mecamylamine, but not by the opioid antagonist naloxone





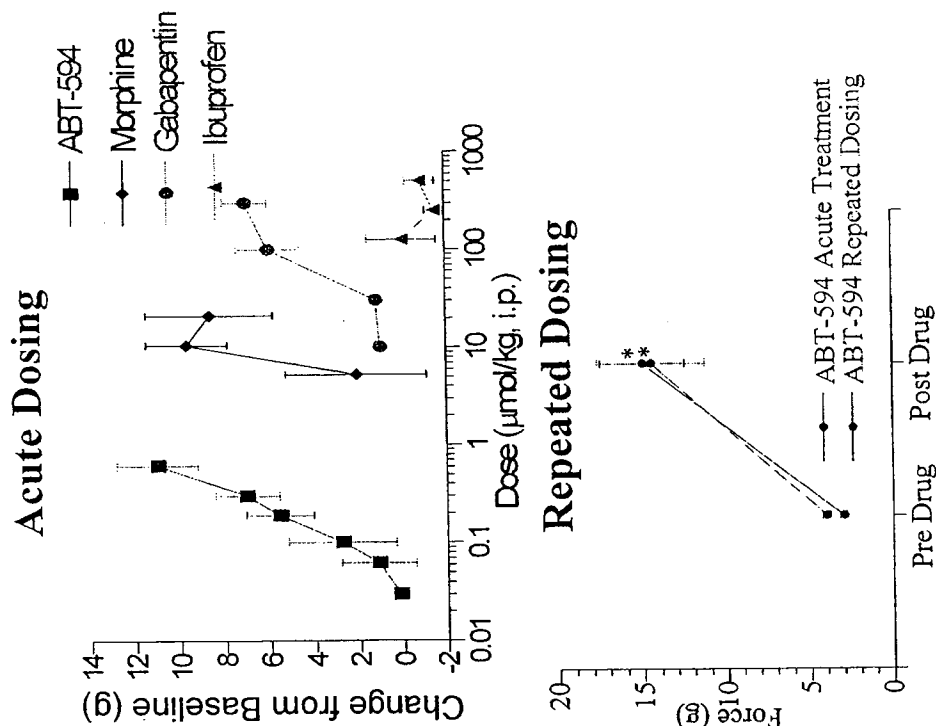
# ABT-594: In Vivo Efficacy in Models of Persistent Pain

- ABT-594 exhibits comparable efficacy and 50-fold greater potency than morphine in Phase II of the formalin model of persistent chemical pain
- ABT-594 is active upon both i.p. and oral administration



# ABT-594: In Vivo Efficacy in Models of Neuropathic Pain

- ABT-594 exhibits comparable efficacy and enhanced potency vs. known efficacious agents in models of neuropathic pain
- Efficacy observed at ~ 3 ng/ml
- ABT-594 retains efficacy following repeated administration
- Efficacy observed in rodent model of diabetic polyneuropathy



# ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
<b>ABT-594</b>	+++ (0.08 $\mu$ mol/kg)	+++ (0.1 $\mu$ mol/kg)	+++ (0.03 $\mu$ mol/kg)
<b>Celecoxib</b>	++ (30 $\mu$ mol/kg)	+ (30 $\mu$ mol/kg)	0
<b>Morphine</b>	+++ (3 $\mu$ mol/kg)	+++ (10 $\mu$ mol/kg)	++ (3 $\mu$ mol/kg)

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

## How do NNR Agonists Produce Analgesia?

- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

# ABT-594: Preclinical Assessment of Side Effect Liabilities

- Emesis
  - Emesis observed in monkey at 9x efficacious plasma levels
  - Emesis observed in dogs at efficacious plasma levels
  - Ferret model developed in response to early clinical data
    - Correlation established between activity at  $\alpha 3\beta 4$  NNRs and emesis
- CV
  - No effects on hemodynamics at 30X efficacious plasma levels
- Dizziness: no validated preclinical models exist
  - Effects on balance, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing
- ABT-594 displays a reduced propensity for morphine-like side effects of:
  - Constipation
  - Respiratory Depression
  - Sedation

## ABT-594: Summary of Preclinical Findings

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NNRs and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
  - Constipation
  - Respiratory depression
  - Sedation
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

# **ABT-594 Project Review February 2, 2001**

## **Clinical Overview**

**Bruce McCarthy**

# ABT-594

## *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need



# ABT-594

**Definitely NOT a take home  
message for today:**

*ABT-594 will satisfy the unmet medical need  
in pain management*

# PART 2

**ABT-594**

## **Clinical development**

### **❖ Current pain management**

- Development strategy: bench to bedside
- Clinical trial results

# Classification of Pain

## Pain Categories

### Nociceptive

#### Acute

Post-dental & post-surgical Pain  
Trauma  
Pancreatitis  
Infections

#### Chronic

Osteoarthritis  
Rheumatoid arthritis  
Fibromyalgia  
Chronic viscearal pain

Dysmenorrhea  
Renal/biliary colic  
Infections  
Tendonitis  
Bursitis  
TMJ disorder  
Sickle cell disease  
Cancer pain  
Rheumatoid arthritis  
Back pain

### Neuropathic

#### Chronic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug induced polyneuropathy  
HIV predominantly sensory neuropathy

Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
CRPS type I and II  
Atypical facial pain  
Phantom limb pain

Cancer pain  
Back pain

# Classification of Pain

## *Pain Epidemiology*

- **Chronic pain**

- 20% U.S. population: any chronic
- 22% worldwide: persistent pain

- **Neuropathic pain**

- 20% of diabetics
- 40% of HIV infected
- 36% of cancer

# Nociceptive Pain

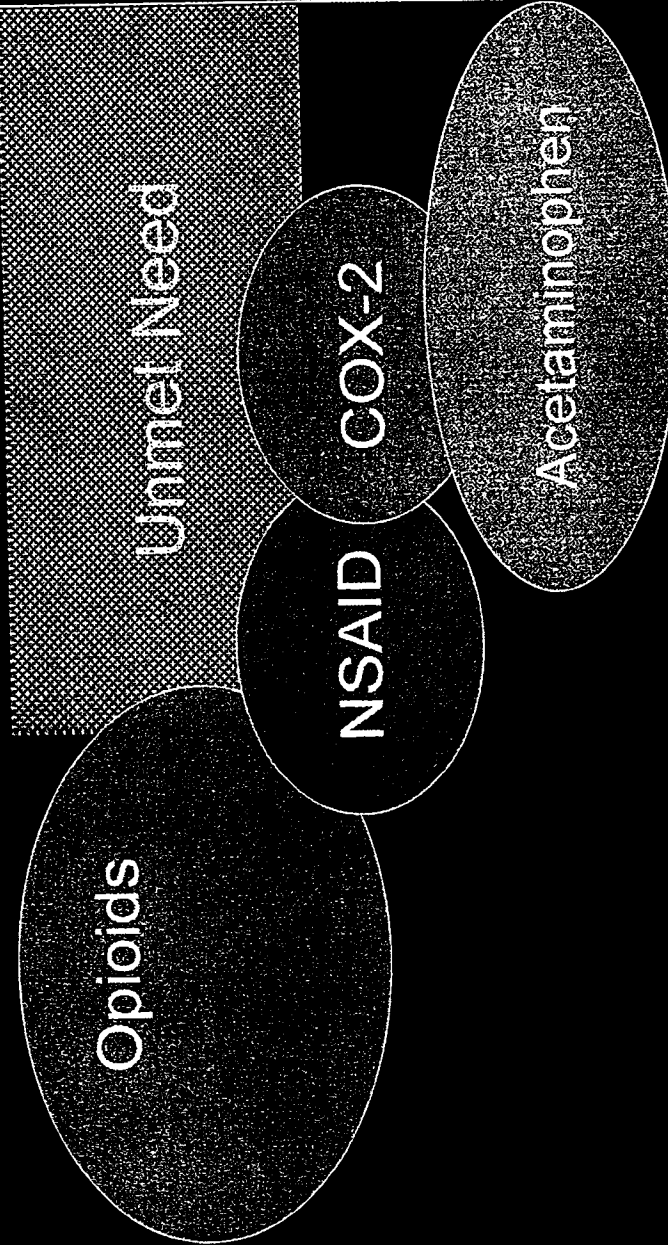
## Treatment

Pain Severity ↑

Severe

Moderate

Mild



Good

Tolerability

Poor

# Nociceptive Pain

## Treatment Adverse Events

Event	Ultram <sup>1</sup> 50-100 mg	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12
Somnolence	N/A	23 %	27%
Dizziness	31%	13 %	20%
Nausea	34%	23 %	41%
Vomiting	13%	12 %	23%
Constipation	38%	23 %	32%
Pruritis	N/A	N/A	16%

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

N/A - Not Available

HIGHLY  
CONFIDENTIAL

ABBT 0002396

# Neuropathic Pain

## *Overview*

- **Characteristic symptoms**
  - Spontaneous: dysesthesia, shooting pains
  - Evolved: allodynia, hyperpathia
- **Pathophysiology**
  - Associated with peripheral nerve injury
  - Abnormalities develop over time in the PNS and CNS
- **Treatment**
  - Tricyclic and other “antidepressants”
  - Antiepileptic drugs
  - Sodium channel blockers (lidocaine)
  - Opioids
  - All minimally effective



# Neuropathic Pain

## *Treatment*

Level of Efficacy

100%

50%

Unmet Need

Tricyclics  
AEDs

Tramadol

Gabapentin  
Pregabalin

Poor

Tolerability

Good

# Neuropathic Pain

## *Treatment Adverse Events Rates*

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A	8%	5%
Somnolence	66%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)

N/A - Not Available

# ABT-594

## Clinical development

- Current pain management

## Development strategy: bench to bedside

- Clinical trial results

**ABT-594**

*Proof of Principle*

**What characterizes an innovative analgesic?**

Spectrum of activity

Time of onset/duration

Level of efficacy

Safety/efficacy ratio

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ABBT 0002401

# ABT-594

## *Spectrum of Activity: Where to Start?*

### Acute

Post-dental surgery  
Sprains and strains  
Acute back pain  
Trauma  
Post-general surgery  
Post-orthopedic surgery  
Dysmenorrhea  
Renal colic  
Biliary colic  
Pancreatitis  
Infections

### Neuropathic

Diabetic polyneuropathy  
Idiopathic polyneuropathy  
Alcoholic polyneuropathy  
Drug-induced polyneuropathy  
HIV predominantly sensory neuropathy  
Back pain  
Cancer pain  
Trigeminal neuralgia  
Post-herpetic neuralgia  
Thalamic pain syndromes  
Spinal cord injury  
Multiple sclerosis  
Complex regional pain syndromes (I, II)  
Atypical facial pain  
Phantom limb pain

### Chronic Nociceptive

Osteoarthritis  
Chronic back pain  
Rheumatoid arthritis  
Cancer pain  
Fibromyalgia  
Sickle cell disease  
TMJ disorder  
Bursitis  
Teninitis  
Chronic visceral pain

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ABBT 0002402

# ABT-594

## *Choose Portals of Entry*

Molar  
Extraction



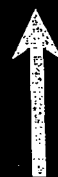
Acute Pain

Peripheral  
Neuropathy



Neuropathic Pain

Osteoarthritis



Chronic Nociceptive  
Pain

# ABT-594

## *Initial Profile*

- **Preclinical promise**

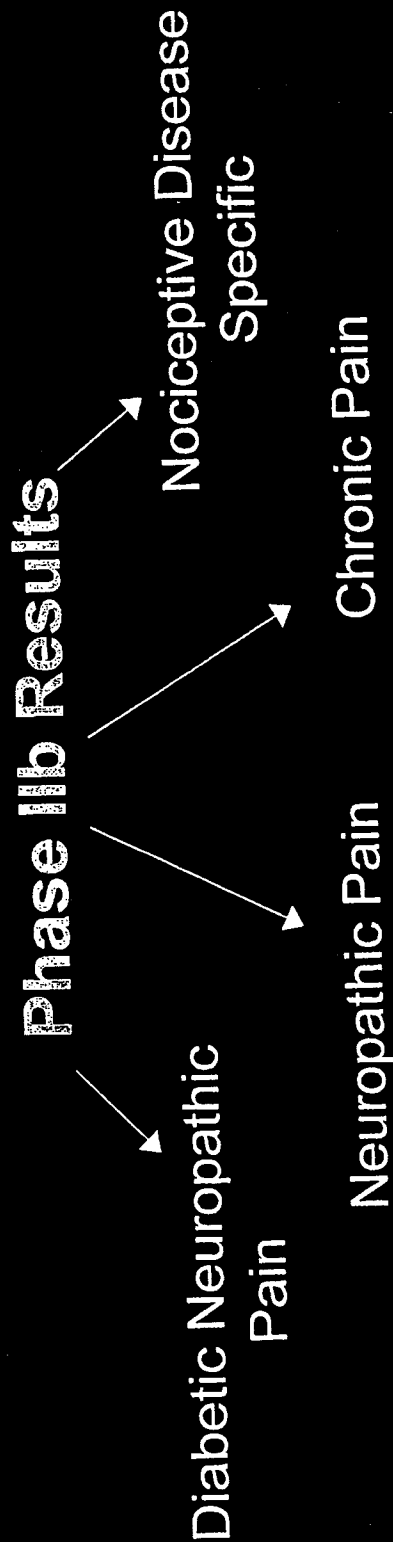
- Efficacy for all types of pain
- Challenges

- **Current characteristics**

- Analgesic potential demonstrated in molar extraction, neuropathic pain and osteoarthritis
- Onset ( $T_{\max}$ , tolerability) appears to exclude rapid relief of pain (“acute pain”)

# ABT-594

## *Future Regulatory Strategy*



### +/- Publication Strategy/Phase IV (e.g.)

- Post-herpetic neuralgia
- Nociceptive pain
  - Osteoarthritis
  - Low back pain

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ABBT 0002406



# ABT-594

## Clinical development

- Current pain management
- Development strategy: bench to bedside

## ❖ Clinical trial results

# ABT-594

## *Pharmacokinetics and Metabolism*

- Half-life ( $t_{1/2}$ ): about 8-12 hours
- Dose proportional kinetics
- AUC,  $C_{\max}$  similar across formulations (solution, SEC, HGC)
- AUC,  $C_{\max}$  similar with/without food
- $T_{\max}$  varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

# **ABT-594**

**ABT-594's analgesic potential demonstrated in:**

**Molar Extraction**

**Neuropathic Pain**

**Osteoarthritis**

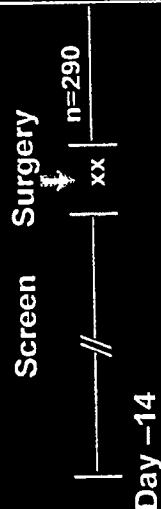
**HIGHLY  
CONFIDENTIAL**

**ABBT 0002408**

# Molar Extraction Study

## Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo
Single dose	

- Third molar extraction
- Outcome measures:

Pain relief (PR)

Categorical scale:

0	1	2	3	4
none	a little	some	a lot	complete

- Power: 70% to detect an effect similar to acetaminophen plus codeine
- Solution

# Molar Extraction Study

## Outcome Measures

- **Pain Relief (PR)**

- Categorical scale:
 

0	1	2	3	4
none	a little	some	a lot	complete

- **Total Pain Associated Relief (TOTPAR)**

- Area under the curve for PR (0-6 hours)

- **Pain Intensity (PI)**

- Categorical scale:
 

0	1	2	3
none	mild	moderate	severe

- Visual Analog Scale



- **Stop Watch Model**

- Time to “perceptible” and “meaningful” relief

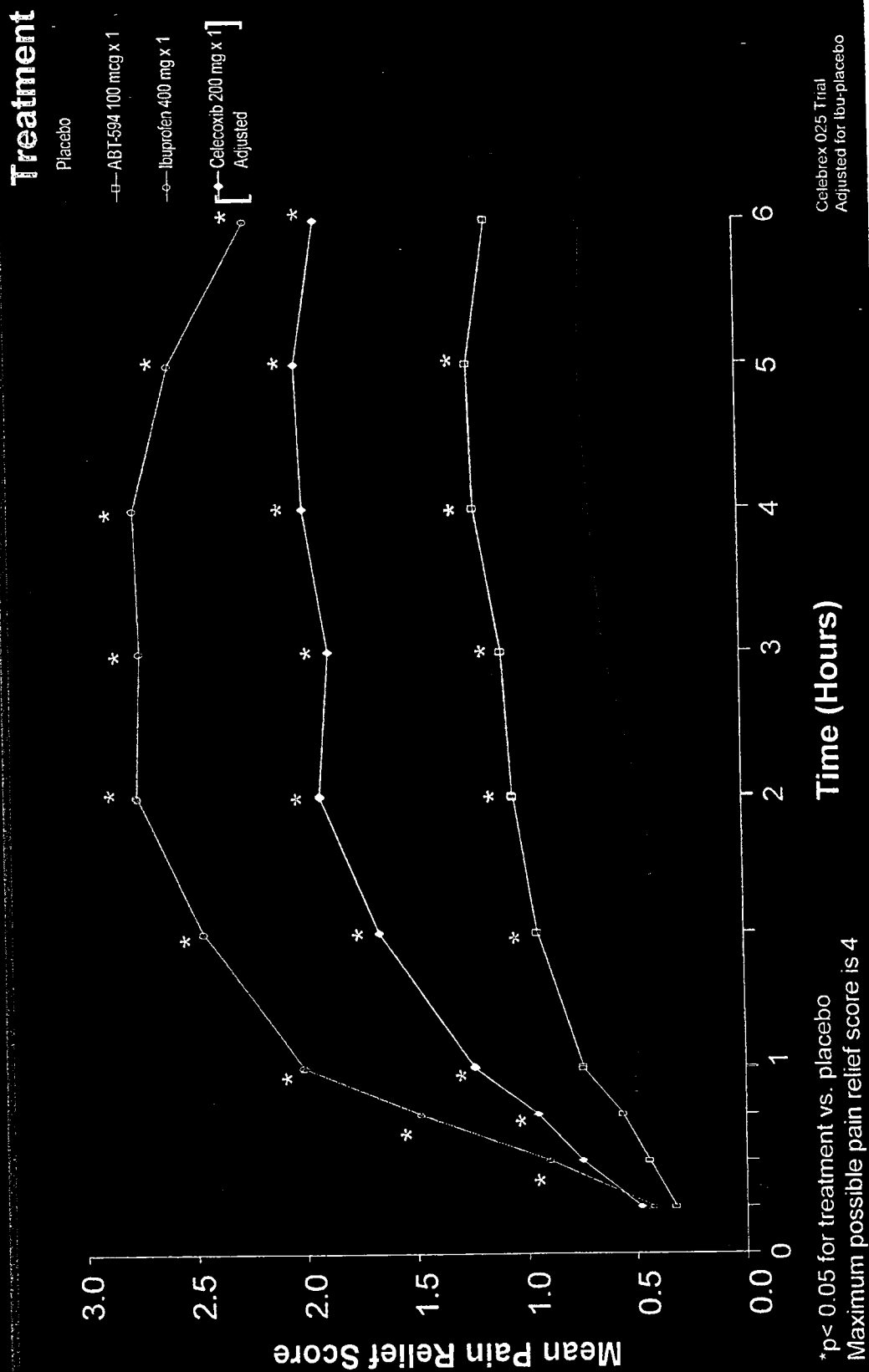
- **Time To Rescue Medication**

- **Patient Global**

- Rate medication:
 

1	2	3	4
poor	fair	good	excellent

# ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



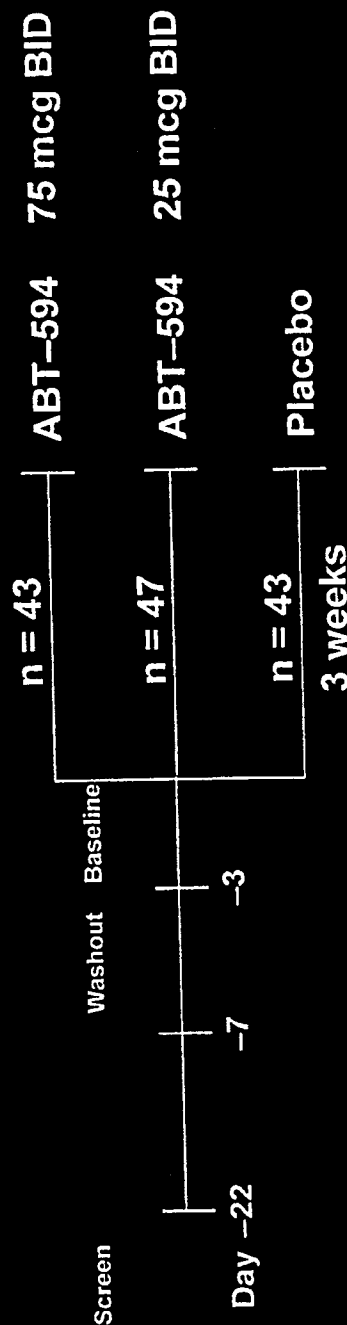
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CONFIDENTIAL

ABBT 0002411

# Neuropathic Pain Pilot

## Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy  
52% idiopathic      46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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CONFIDENTIAL

ABBT 0002412

# Neuropathic Pain Pilot

## Outcome Measures

### • Pain Intensity (PI)

- Categorical Scale:
- Visual Analog Scale: (0-100 mm)



### • Neuropathic Pain Scale (NPS)

- 10 items (e.g., sharp, hot, intense), for total 0-100 points
- Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10	The most sharp sensation imaginable ('like a knife')
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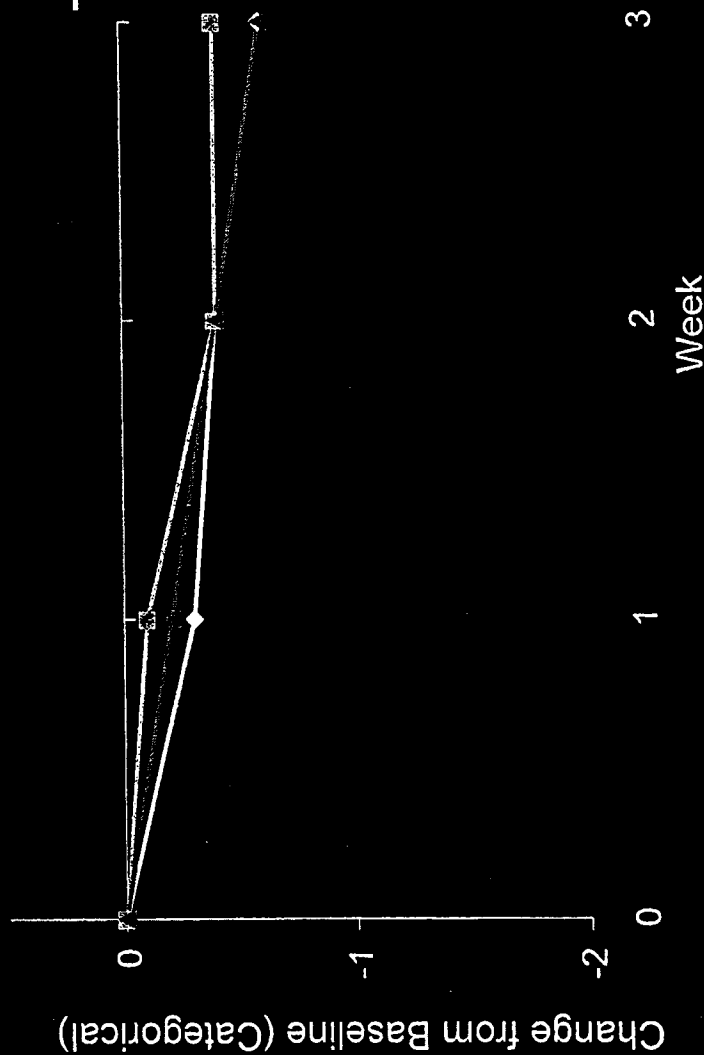
### • Patient Global (PG)

- Rate Medication:
- |      |      |      |           |
|------|------|------|-----------|
| 1    | 2    | 3    | 4         |
| poor | fair | good | excellent |



# ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain

Treatment	Change: Baseline to Final
Placebo	↓ 25%
ABT-594 25 mcg BID	↓ 14%
ABT-594 75 mcg BID	↓ 28%



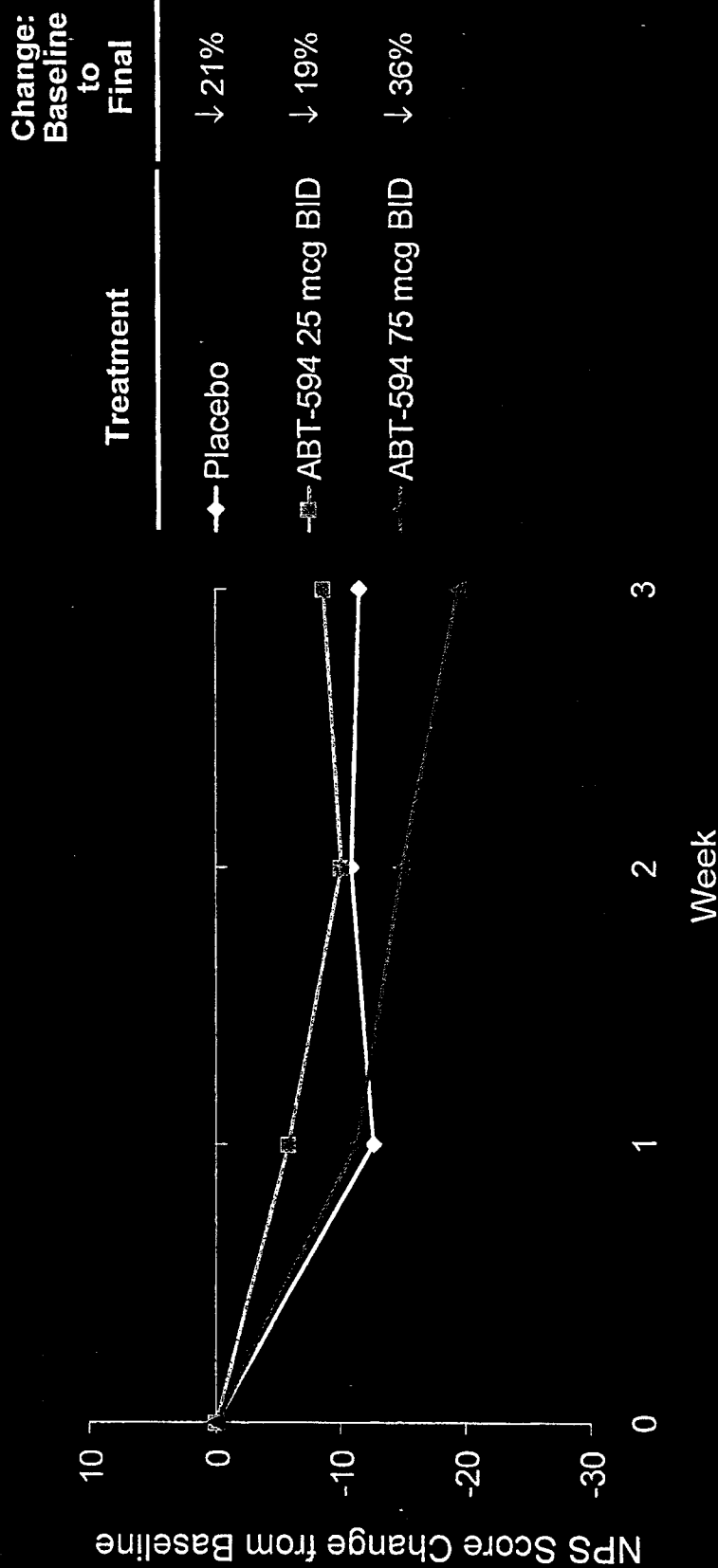
Maximum possible decrease for 75 mcg BID was 2.5

Model based, ITT  
LOCF  
833

HIGHLY  
CONFIDENTIAL

ABBT 0002414

# ABT-594 75 mcg BID Reduces the NPS More Than Placebo



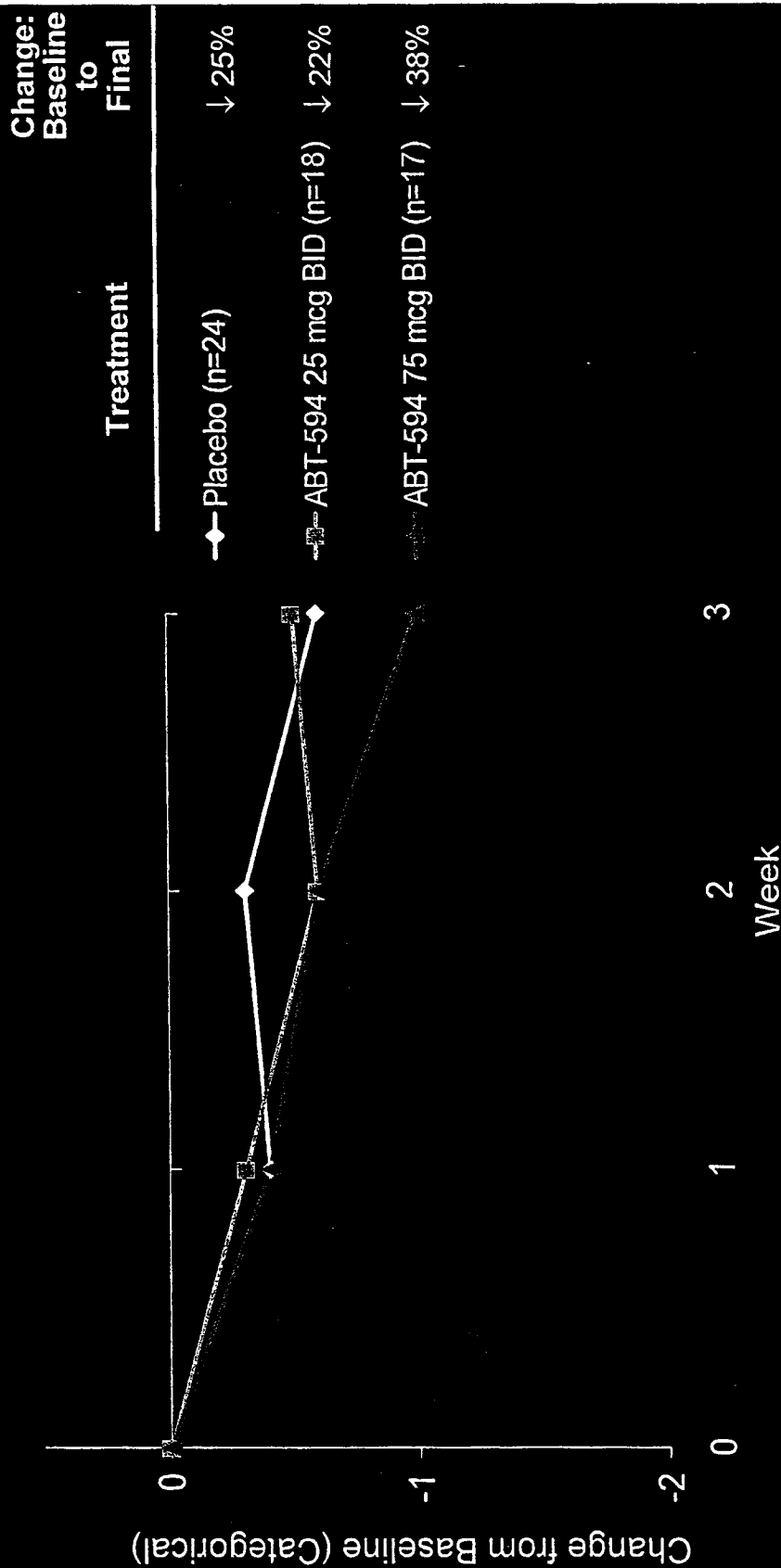
Maximum possible decrease for 75 mcg BID was 59

Model Based, ITT  
LOCF  
833

HIGHLY  
CONFIDENTIAL

ABBT 0002415

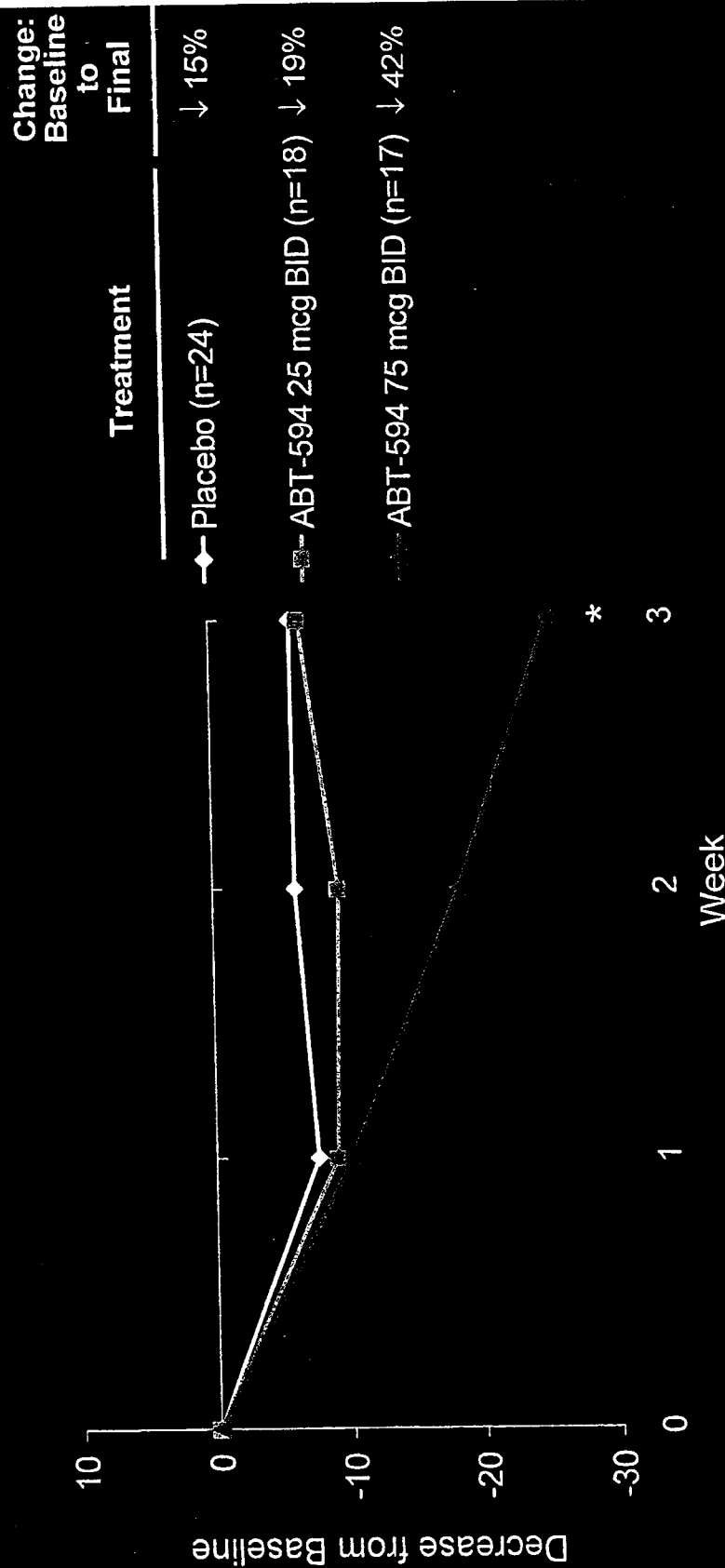
# ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy



Maximum possible decrease for 75 mcg BID was 2.6

Model based, ITT  
LOCF  
833

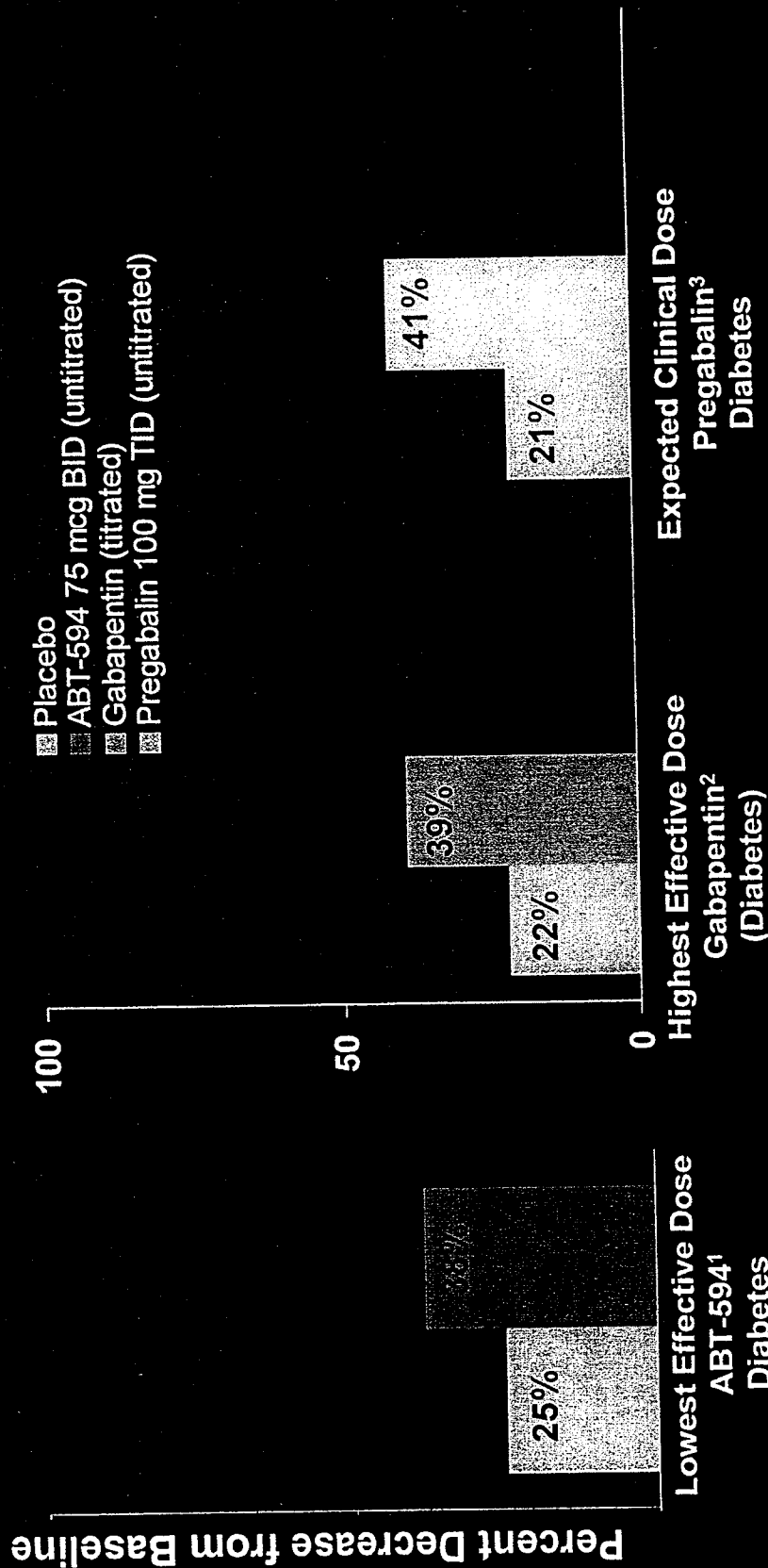
# ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy



Model Based, ITT  
LOCF  
833

# ABT-594 75 mcg BID has a Similar Effect To Gabapentin

## ABT-594 vs. Gabapentin and Pregabalin

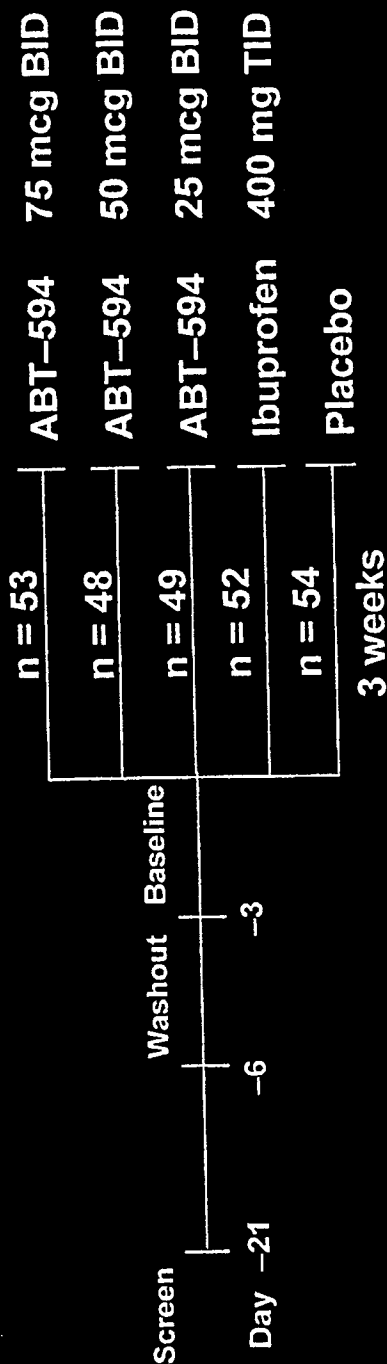


<sup>1</sup> 4-point categorical scale final vs. baseline  
<sup>2</sup> 11-point Likert Scale week 8 vs. baseline  
<sup>3</sup> 11-point Likert scale week 5 vs. baseline

# Osteoarthritis Pain Pilot

## Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

HIGHLY  
CONFIDENTIAL

ABBT 0002419

# Osteoarthritis Pain Pilot Study

## *Outcome Measures*

- **Pain Intensity (PI)**

- Categorical Scale:

0	1	2	3
none	mild	moderate	severe

- Visual Analog Scale (VAS):



- **WOMAC**

- Pain (0-500)
  - Stiffness (0-200)
  - Function (0-1700)

Total (0-2400)

- **Patient Global**

- Rate Medication:

1	2	3	4
poor	fair	good	excellent

# Osteoarthritis Pain Pilot Study

## WOMAC

### Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain |

| extreme  
pain

### Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness |

| extreme stiffness

### Function

What degree of difficulty do you have...

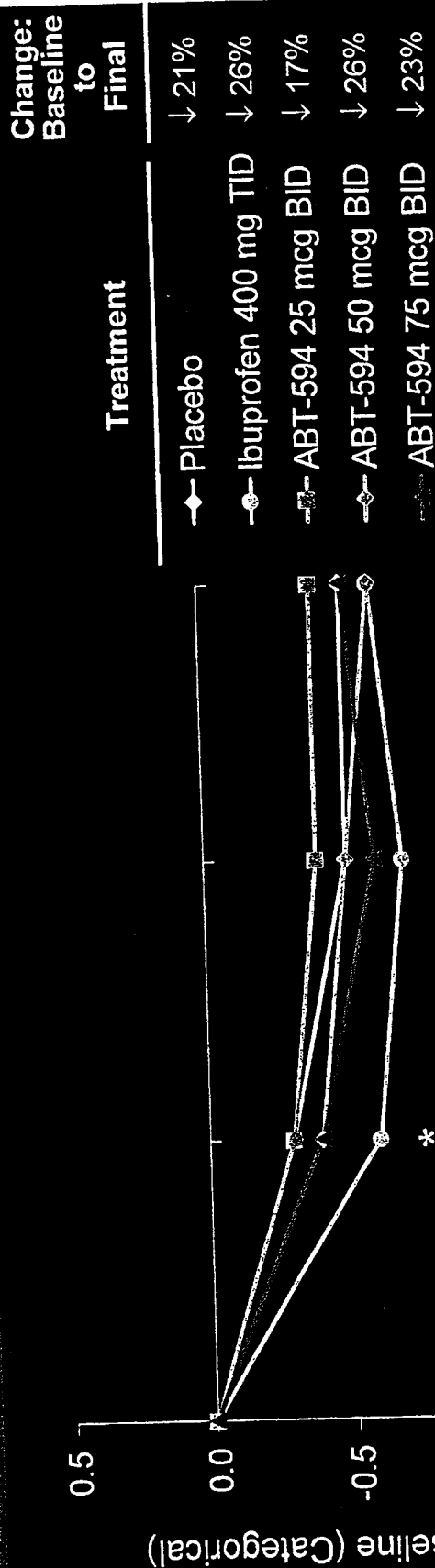
- Descending stairs?
- Rising from bed?

no difficulty |

| extreme difficulty



# ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis



Model based, ITT  
LOCF  
826

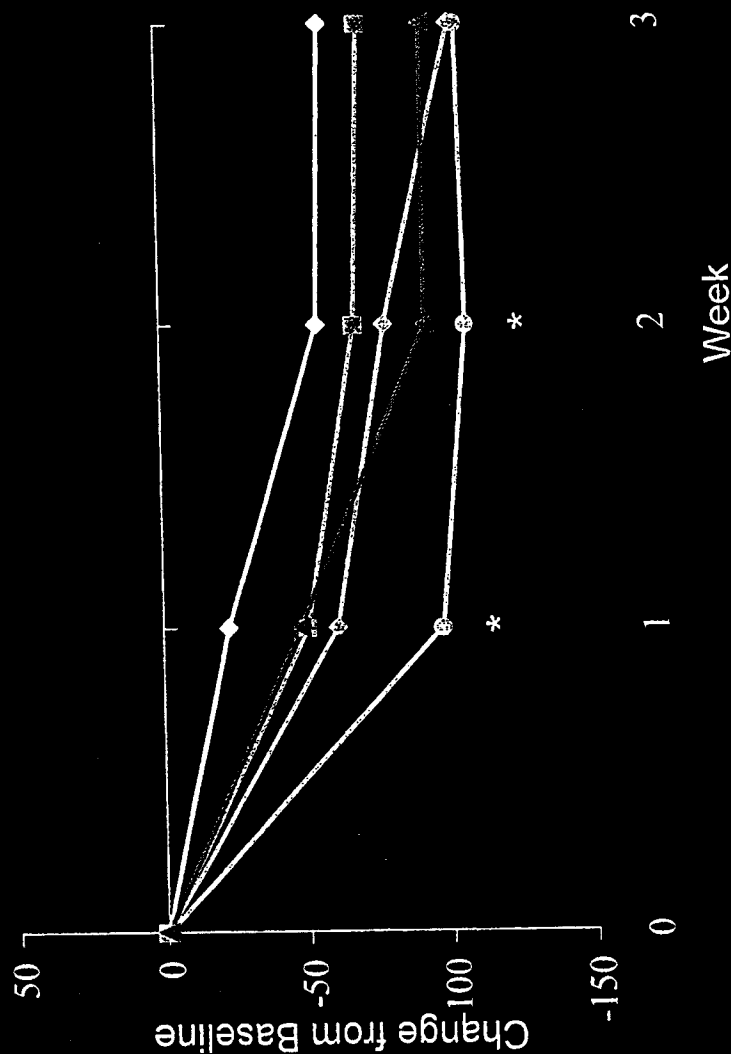
\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 2.2

# ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis

Change:  
Baseline  
to  
Final

Treatment

◆ Placebo	↓ 19%
● Ibuprofen 400 mg TID	↓ 33%
■ ABT-594 25 mcg BID	↓ 24%
◇ ABT-594 50 mcg BID	↓ 34%
★ ABT-594 75 mcg BID	↓ 30%



\*  $p \leq 0.05$  vs. placebo  
Maximum possible decrease for 75 mcg BID was 305

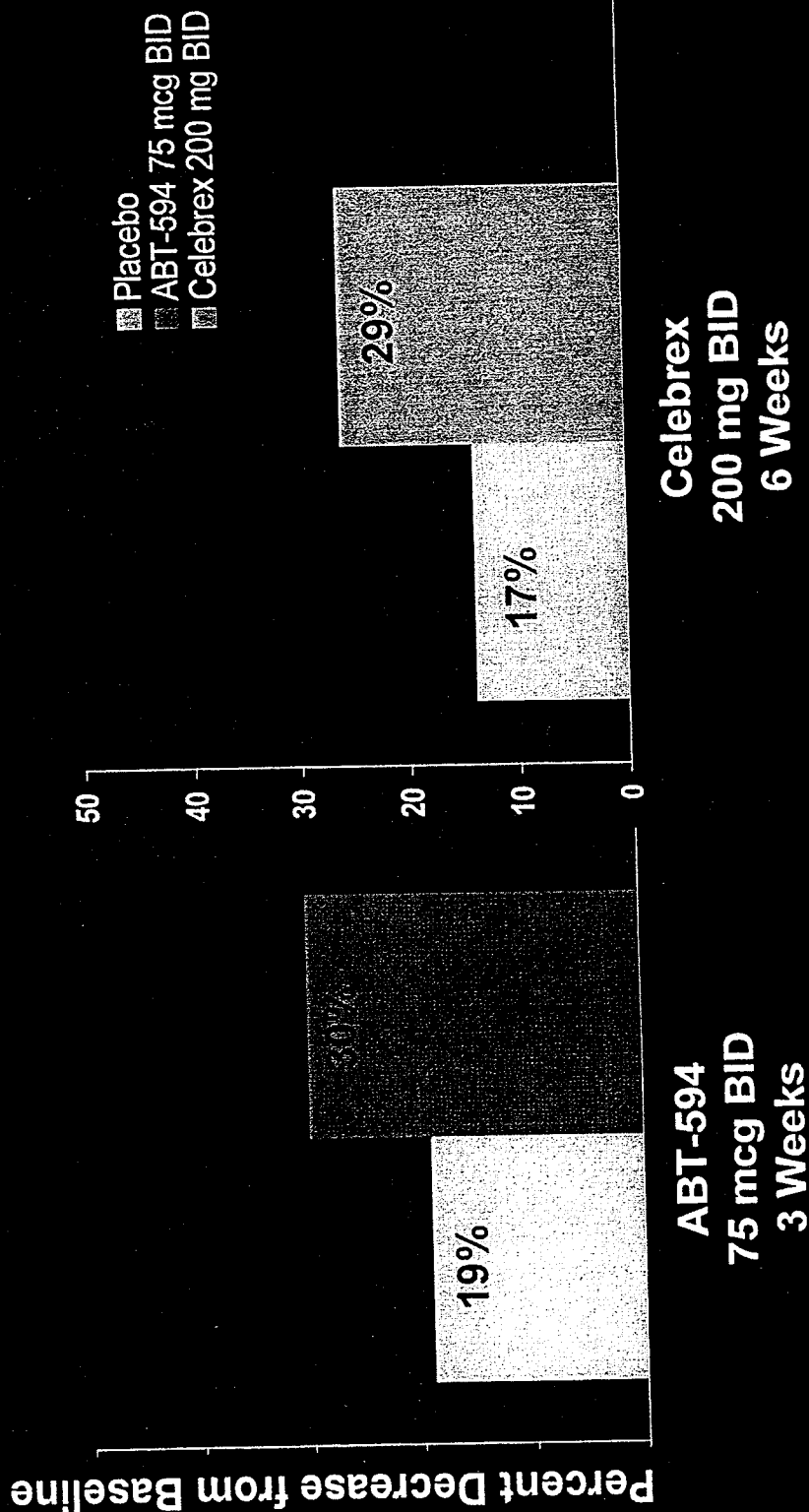
Based on 5-item (0-500 points)

HIGHLY  
CONFIDENTIAL

ABBT 0002423

# ABT-594 75 mcg BID Has An Effect Similar to Celebrex

*WOMAC Pain Decrease from Baseline*



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ABBT 0002424

# ABT-594

## *Phase IIa Efficacy Conclusions*

- Analgesic Potential Demonstrated
  - Molar Extraction
    - Significance vs. placebo starting at 1.5 hours
  - Neuropathic Pain
    - 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy
  - Osteoarthritis Pain
    - 75 mcg BID may be lowest effective dose as judged by the WOMAC pain sub-score

# ABT-594 Safety

## *Phase IIa Adverse Events*

- Characteristic AEs
  - Nausea
  - Vomiting
  - Dizziness
- AEs attenuate after repeated administration

# Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d <sup>1</sup>	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 <sup>2</sup> 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	N/A

<sup>1</sup> Max, 1987 (n=29)

<sup>2</sup> M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002427

# Adverse Event Rates for Select Analgesics

Event	Ultram <sup>1</sup> 50-100 mg q4-6h	OxyContin <sup>2</sup>	OxyContin Osteoarthritis 20 mg q12h	ABT-594 <sup>3</sup> 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

<sup>1</sup> Chronic non-malignant pain, up to 30 days (label)

<sup>2</sup> "Clinical trials" (label)

<sup>3</sup> M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002428

# ABT-594

## *Phase IIa Conclusions*

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
  - SEC tolerated better than predicted by solution
  - 75 mcg BID (HGC) very well tolerated vs. other analgesics
  - Two Phase I studies (M99-076 and M99-120) showed:
    - 300 mcg BID HGC tolerated
    - Titration may improve tolerability
- Full analgesic potential should be defined with adequate dose ranging studies in Phase IIb



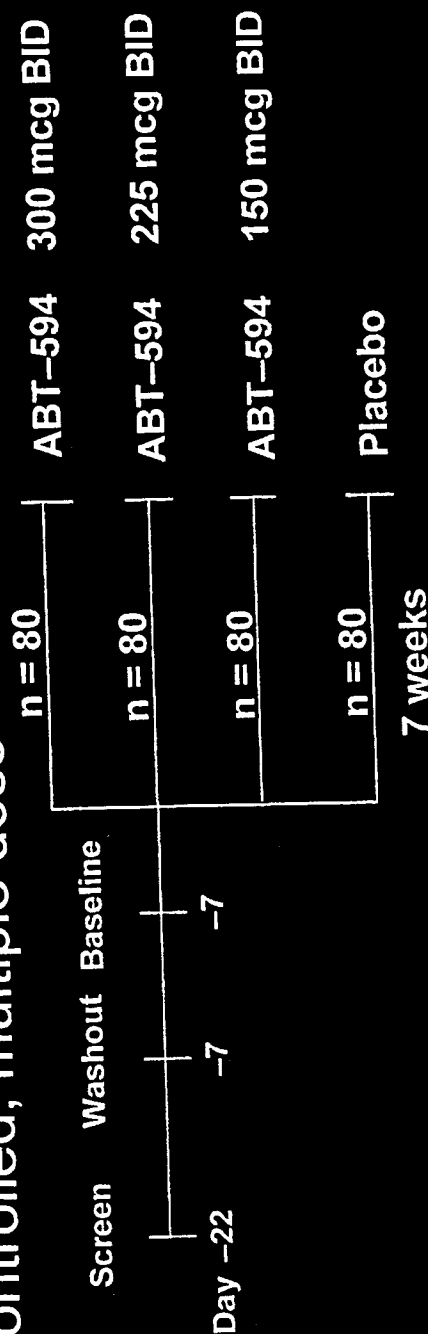
## Phase IIb

- Trials
  - Neuropathic Pain (M99-114)
    - Ongoing
  - Osteoarthritis Pain (M99-115)
    - Unfunded
- Doses
  - 150, 225, 300 mcg BID

# M99-114: Neuropathic Pain

## Design

- 320 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-Day primer phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)
- Hard Gelatin Capsule

# M99-114: Neuropathic Pain

## *Outcome Measures*

- Primary
  - Weekly average of daily pain (11-point Likert in a diary)
- Secondary
  - Site-based pain scale (11-point Likert)
  - Neuropathic Pain Scale
  - Patient Global Impression of Change
  - Physician Global Impression of Change
  - SF-36

## M99-114 Status

- Enrollment
  - Ended 1/5/01 at 269 subjects
  - Pre-specified power not reached
  - Width of confidence intervals not meaningfully different between 269 and 320 enrolled
- Database release – 5/01
- Go/No Go – 6/01

# ABT-594

## *Take Home Messages*

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
  - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

**ABT-594 Project Review  
February 2, 2001  
Commercial Assessment**

**Andrea Landsberg  
Laura Robinson**

**HIGHLY  
CONFIDENTIAL**

**ABBT 0002435**

# **ABT-594 Commercial Assessment: Key Take Aways**

- Neuropathic pain market is the primary target
  - Underserved market with significant unmet need
  - ABT-594 has potential to be first novel drug in decades indicated for neuropathic pain
- Additional opportunity in “chronic persistent pain” market
- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*

# Neuropathic Pain Market: Sales

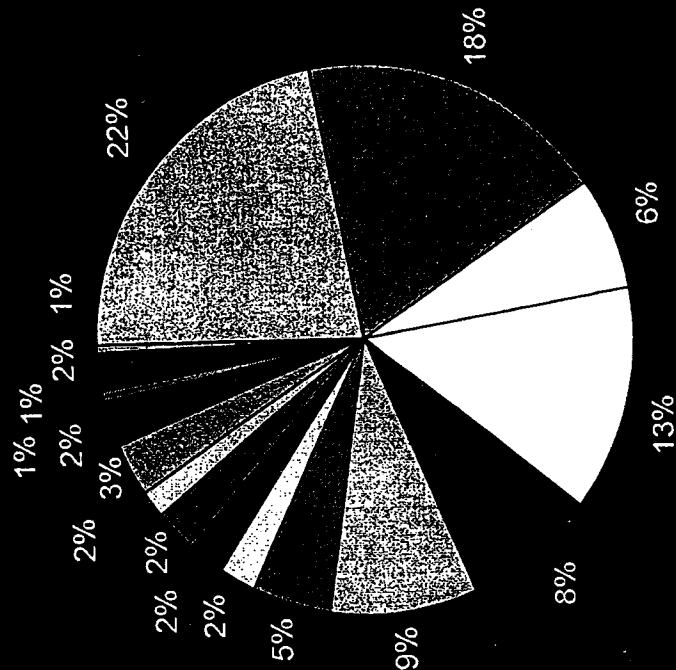
	2000 US Sales (\$MM)	2000 ex-US Sales
AEDs	\$299	\$190
TCAs	\$3	\$45
OPIOIDS	\$37	NA
OTHERS	\$85	\$45
<b>TOTAL</b>	<b>\$424</b>	<b>\$280</b>

US Sales factored for neuropathic pain and annualized  
Vs Prior Year: US Growth est 20%, ex-US growth est 10%



# Drug Classes Used to Treat Neuropathic Pain

*Dispersed market due to limited promotion and lack of dominant effective product*



**Drug Uses Data (not Rx or \$'s)**

SEIZURE DISORDERS
ANTIARTHRICS SYS PLN
COX-2 INHIBITORS
CODEINE & COMB NON-INJ
CORTICOIDS PLAIN INJ
ANTIDEP TRI/TETRA
PTY ANALGESICS
PYRIDOXINE (VIT B6)
SYN NON-NARC NON-INJ
MUSC RLX W/O ANALG
CORTICOIDS PLAIN ORAL
PROPOXYPHENES
ANESTH INJECT LOCAL
ASPIRIN,APC,ETC
SSRI'S/SNRI'S
ACETAMINOPHEN
BENZODIAZEPINES

## Use in Neuropathic Pain

- Even if target only 'focused' indication in 'painful, diabetic neuropathy' expect trial and usage in all types of neuropathic pain
  - Neurontin use all off-label
  - Carbamazepine is indicated for trigeminal neuralgia but used in all neuropathic pain
  - Generally held premise that NP likely has some similar mechanisms across etiologies (reinforced by current drug usage)

# Market Opportunities in Neuropathic Pain

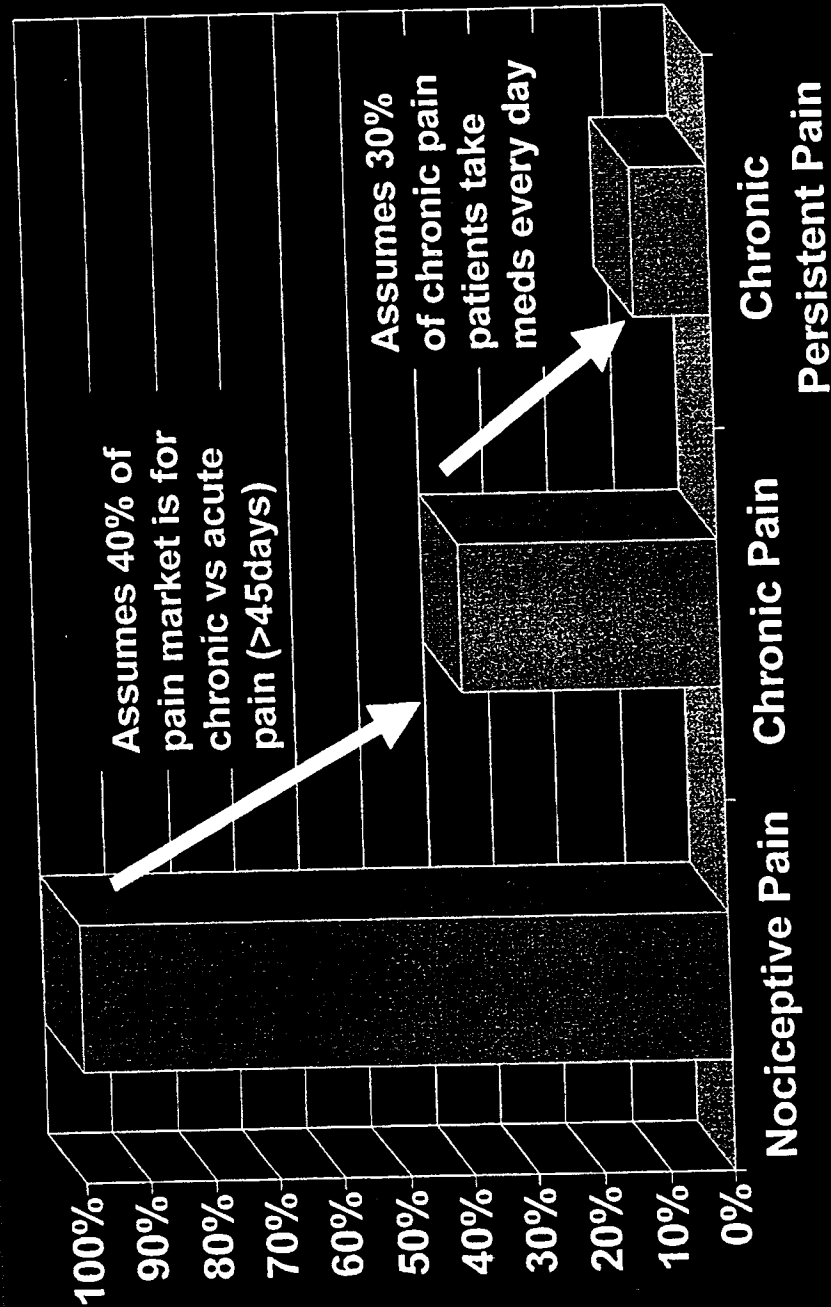
- Improved efficacy
  - Partial pain relief is the norm
  - Polypharmacy often required to manage pain
- Improved responder rates
  - Typically only 40% to 60% of patients respond to any given treatment
- Improved tolerability over time
  - TCAs, AEDs, opioids have troublesome SEs that do not diminish over time
- Dose reduction
  - Most TCAs and AEDs (including Neurontin) typically dosed TID
- Titration reduction
  - TCAs and AEDs require >2 weeks titration period to minimize SEs or reach effective dose

# PART 3

# Chronic Persistent Pain (CPP) “Spillover”

- Onset of action and need for titration limits ABT-594 to a small segment of the nociceptive pain market
- CPP = Chronic persistent pain conditions for which patients are on daily medications, over extended periods of time (vs. PRN, or ‘as needed’, consumption)

# Chronic Persistent Pain



IMS Longitudinal Data indicates over 80% of pain meds Rxed for  $\geq 30$  days  
Quantitative primary market research indicates that  $>60\%$  of chronic pain patients take meds every day

# Chronic Persistent Pain Market

	1999 Sales (\$MM)	CAGR (97-99)	Rxs (MM)	CAGR (97-99)
US	\$700	5%	35	1%
Ex-US	\$680	8%	58	3%

## CPP Market Size Assumptions:

Assume 40% of opioid, non-opioid, COX-2 market is for chronic pain and 30% of that is 'persistent', i.e.: medication taken every day

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

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# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent			
Same	Equivalent			
Better	Poor			

TCAs used as "benchmark" efficacy in NP

Tolerability vs. current agents: equivalent = 5% nausea; 5% vomiting; 10% dizziness; poor = 20% nausea; 10% vomiting; 30% dizziness

# Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent	19%	12%	16%
Same	Equivalent	15%	8%	10%
Better	Poor	12%	6%	11%

*Spillover market share in chronic persistent pain markets (in forecast, assuming only 5% share)*

*MR did not test impact of titration on market share*

# Qualitative Market Research Results

Profile		Share of Patients
Efficacy	AEs vs. current agents	Neuropathic Pain
Better	Equivalent	31%
Better	Poor	24%
Same	Equivalent	27%

*Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain*

*In forecast assuming 20% share of NP*

# Neuropathic Pain Pipeline

- Pregabalin is in Phase III, but questions remain regarding Pfizer's Neurontin/Pregabalin strategy
- 4 NNR preclinical programs appear to be targeting pain indications; ABT-594 is much further along
- Other new AEDs may have potential for treatment of neuropathic pain and are conducting phase IV trials; unclear whether these agents will pursue an NP indication
- Several novel pain mechanisms being explored
  - Calcium channel blockers
  - Sodium channel blockers
  - NMDA antagonists

## **Positioning of ABT-594 in Neuropathic Pain**

- Greater efficacy than AEDs and TCAs in NP
- Better long term tolerability (than TCAs and opioids)
- Safe in all patient populations
- Convenient BID dosing with simple, short titration period
- No tolerance over time and non-scheduled
- Limited drug interactions
- Novel mechanism of action

# Positioning of ABT-594 in CPP

- Effective alternative to opioids with:
  - No tolerance, respiratory depression, constipation, etc.
  - Non-scheduled
- For patients receiving insufficient relief with current therapies or NSAID/opioid intolerant patients
- Better efficacy than COX-2s with novel mechanism of action and no major safety issues

# ABT-594 Global Forecast Ranges

	Peak Sales (\$MM)		
	Low	Base	High
US	\$92	\$339	\$509
Ex-US	\$130	\$363	\$712

- NP shares: 5%, 20% or 30%
- CPP shares: 3%, 5%, 7%

# Key Product Challenges

- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*
  - Neurontin/Pregabalin may have advantage
    - Will need to minimize early DCs as much as possible
  - Potentially low therapeutic index
- **Titration**
  - Schedule must be as short and simple as possible
- **Nicotinic mechanism**
  - Will require pre-launch market education and priming to diffuse negative associations and generate interest surrounding novel MOA



**Go/No Go Process**

**Bruce McCarthy**

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**ABBT 0002453**

# ABT-594

## *Go/No Go Process*

### The Challenge

Integration of many interrelated data

Efficacy

Safety

Dose Response

Pharmacodynamics

Dose Selection

Phase III Trial Design

Titration Effects

Indications

Market Research

Segmentation

Targeting

Positioning

### The Plan

Leverage decision analysis (DSG) as a process  
to determine Go/No Go criteria

# ABT-594

## *Go/No Go Process*

### **Process to include:**

1. Scope and frame issues and process
2. Analysis of M99-114 and other clinical data
3. Dose identification
4. Draft Phase III trial design
5. Market research
6. Valuation
7. Presentation and asset strategy: 6/01

Decision Analysis —→

# ABT-594

## *Go/No Go Process*

### What will a “Go” decision look like?

Patients and physicians will have compelling reasons to choose ABT-594 vs. other analgesics for the relief of pain

# **ABT-594 Project Review February 2, 2001**

## **Follow-On Strategy**

**Mike Meyer**

# Identification of ABT-594 Backup

## *Clinical Results Outline Specific Improvements Required for Backup*

- Emesis
  - Modeled preclinically in ferret and dog
- Nausea
  - Ferret model can qualitatively address nausea index
- Dizziness
  - Mouse rotarod
  - Rat Edge test

# Discovery Program Basis

## *NNR Subtypes Differentially Mediate Efficacy and Side Effects*

- Different NNR subtypes mediate analgesic effects of nicotinic agonists and adverse events
- Program committed to the identification of NNR subtype selective compounds
- Project initiated research collaboration with NeuroSearch (Denmark)
  - Access to human recombinant NNRs
  - Access to new structural classes of NNR modulators

# Nociception Mediated by $\alpha 4$

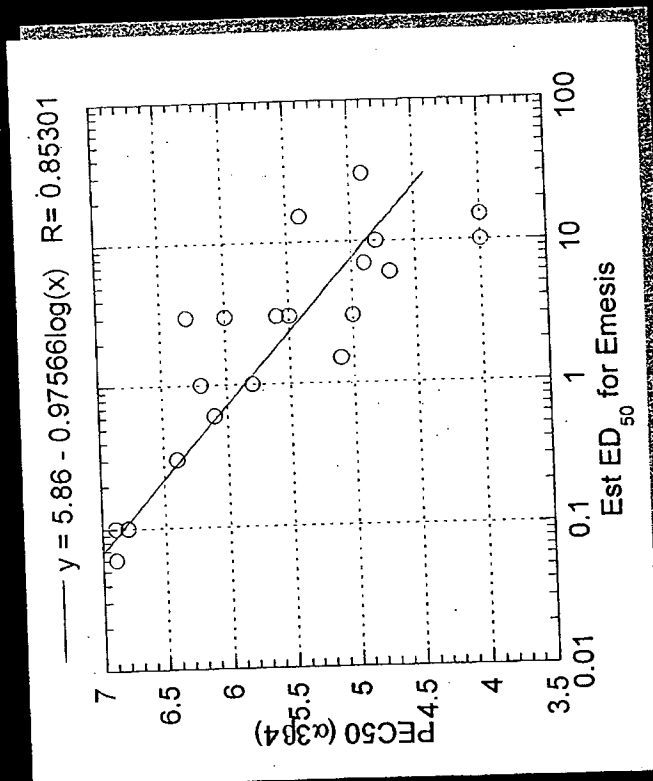
## Subtypes

- Mouse knockouts support role of  $\alpha 4$  and  $\beta 2$ 
  - Key differences between pain type
- Role for  $\alpha 4$  subtype in acute thermal pain (activation of descending inhibitory pathways)
  - Antisense studies
  - Site injection studies
  - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated



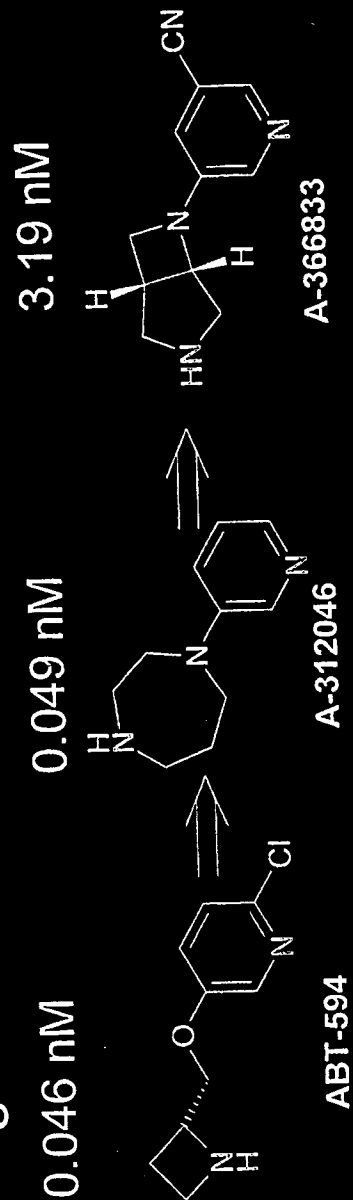
# Emesis Mediated by $\alpha 3\beta 4$ Subtype

- In preclinical models, emesis is correlated to potency and efficacy at ganglionic ( $\alpha 3\beta 4$ ) NNR subtypes
- Antagonist and route of administration studies suggest both local and systemic contribution

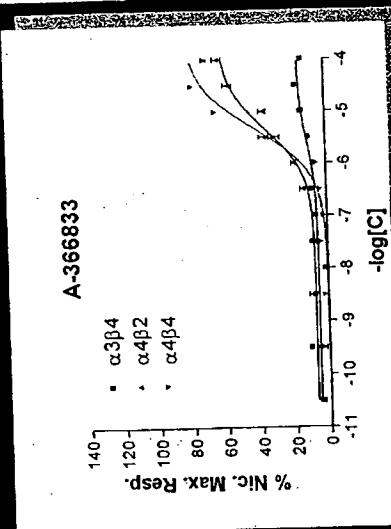
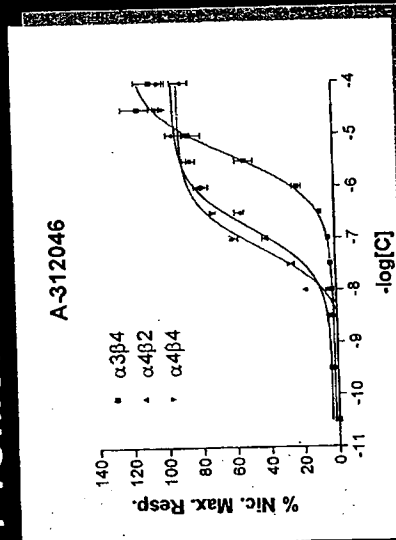
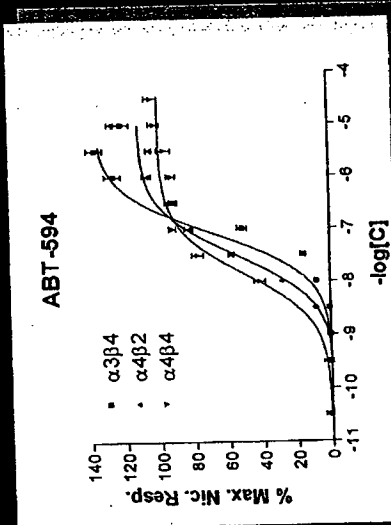


# $\alpha$ 4-Selective Ligands: In Vitro Profile

## • Radioligand Binding Profile:



## • In Vitro Functional Profile:



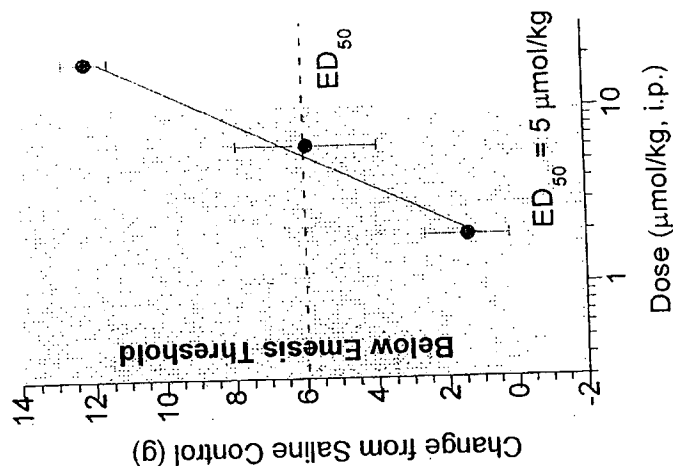
# Analgesic Efficacy vs. ABT-594 (Rat Models)

	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 $\mu$ mol/kg)	+++ (0.1 $\mu$ mol/kg)	+++ (0.03 $\mu$ mol/kg)
A-312046	+++ (1.8 $\mu$ mol/kg)	+++ (0.7 $\mu$ mol/kg)	+++ (1.9 $\mu$ mol/kg)
A-366833	+++ (3 $\mu$ mol/kg)	+++ (5 $\mu$ mol/kg)	++ (6 $\mu$ mol/kg)
Celecoxib	++ (30 $\mu$ mol/kg)	+	0
Morphine	+++ (3 $\mu$ mol/kg)	+++ (10 $\mu$ mol/kg)	++ (3 $\mu$ mol/kg)
Gabapentin	+	++ (100 $\mu$ mol/kg)	0

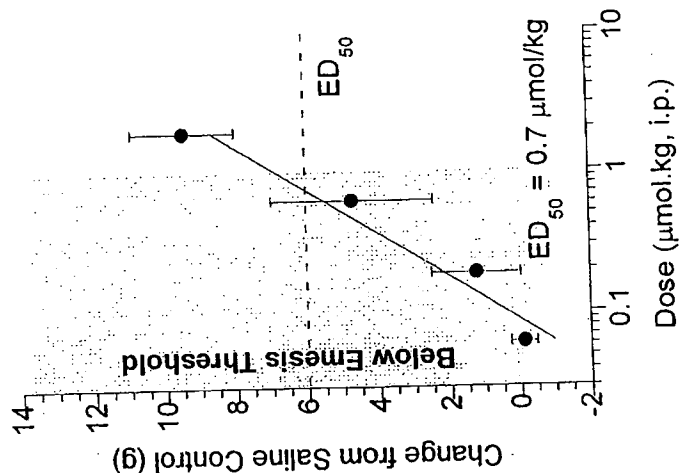
+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

# Efficacy Indexed to Emesis Liability (Neuropathic Pain)

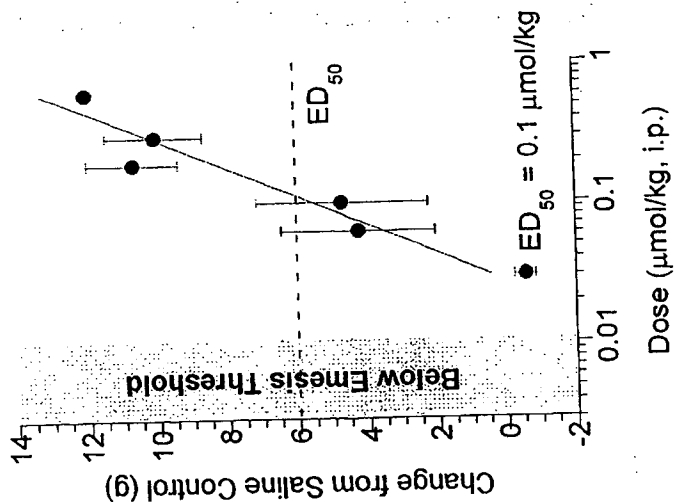
A-366833



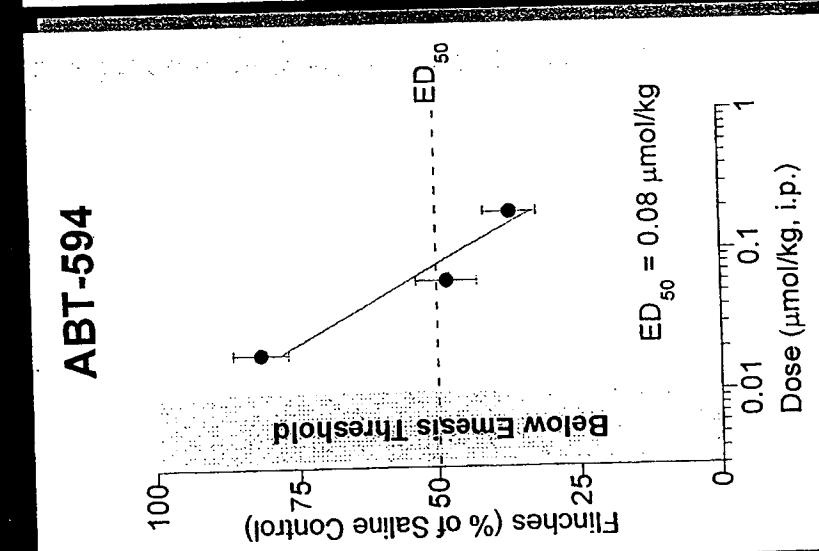
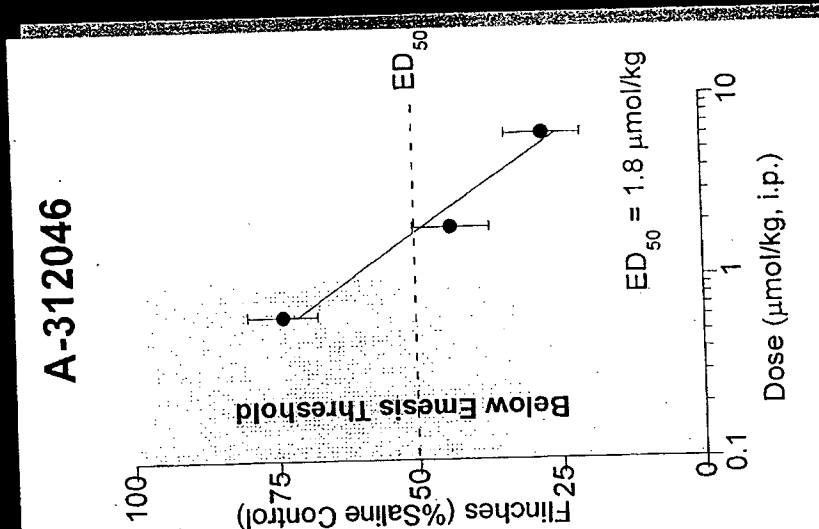
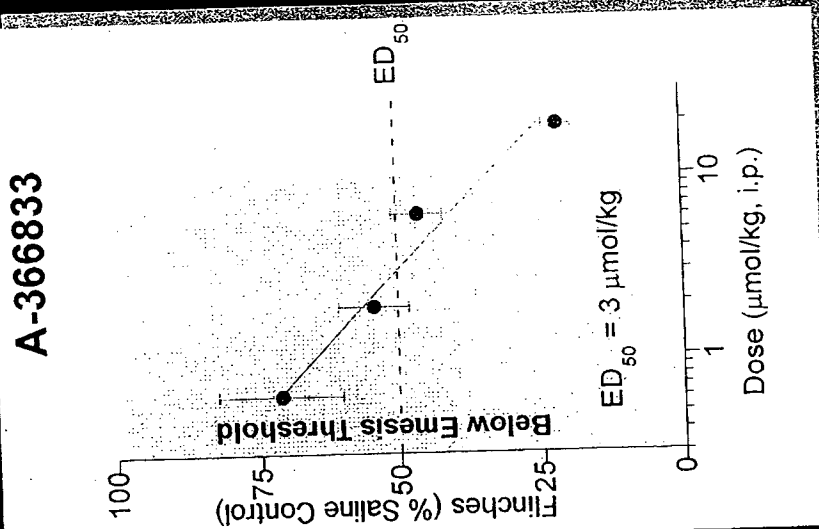
A-312046



ABT-594



# Efficacy Indexed to Emesis Liability (Nociceptive Pain)



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# Therapeutic Index Comparison

- Therapeutic index based on ratio of highest no effect dose for adverse event and ED<sub>50</sub> in pain models

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5 - 14x	20 - 27x
Seizure Threshold (Mouse)	4 - 11x	>11x
Edge Test (Rat)	7 - 24x	>12x

# Pharmacokinetics

**t<sub>1/2</sub>      CLp      %F**

Rat	1.5 h	1.7	61%
Dog	4.7 h	0.4	35%
Monkey	1.4 h	1.7	80%
Rat	3.0 h	1.95	80%
Dog	1.4 h	2.89	13%
Monkey	1.5 h	2.36	3%
Rat	1.5 h	3.02	73%
Dog	2.6 h	0.35	109%
Monkey	2.5 h	0.53	74%

**ABT-594**

**A-312046**

**A-366833**

## Additional Characterization and Ongoing Studies

- A-312046:
  - Evaluation of viability of transdermal formulation
  - Identification of prodrug analogs
- A-366833:
  - Ames and chromosomal breakage neg.
  - CEREP binding studies – no significant findings
  - Ongoing studies:
    - Evaluation in additional pain models
    - PK/PD studies – plasma levels at efficacious and emetic doses
    - Dog, monkey, human hepatocyte metabolism
    - Cardiovascular evaluation
    - Two-week toxicology in rats



## Backup Status

- A-366833:
  - Broad spectrum activity, but particularly effective in persistent nociceptive pain model
  - Significantly decreased side effect liability
  - Excellent oral bioavailability across three species
  - May extend into general pain indication
- A-312046:
  - Excellent activity in neuropathic pain model
  - Pharmacokinetics may preclude development as oral drug
  - Alternative formulations may be useful as backup for ABT-594 in neuropathic pain market





A B B O T T

From: Mike Comilla  
 Supervisor, FP&A  
 D404, AP9 Ext. 7-1065  
 Date: December 21, 2000

TO: Distribution

RE: 2001 PLAN ASSUMPTION MEMO- Pass III

This package contains assumptions for the 2001 PLAN (Pass III). The assumptions are based on input from the respective project managers and specific questions regarding the projects may be directed to the contacts listed below.

Please input requirements for 2001 project manpower, functional expense and headcount. Guidelines for the functional input are:

- Payroll/ Merit Increase: Exempt 4% Non-Exempt 4%
- Fringe benefit rates as a % of payroll dollars (excluding profit sharing and bonus):  
     Exempt 35.2%      Non-Exempt 38.7%      Temporary 9.0%

Please give equal attention to forecasting Blue Plan (BP) projects, as these budgets will be used if additional funding becomes available.

To meet divisional planning requirements, all data must be input by **noon, January 10, 2000**. Key Program activities are summarized below and detailed assumptions are attached.

**DISCOVERY:**

Contact: Ellie Haapala (7-1403)

-Please contact Ellie Haapala (7-1403) with any Discovery budget questions.

**DELIVERY (GLOBAL):**

**COX II ABT-963** (*Attachments A*)

Contact: George Carter 7-8109

- G0-414.030 Only those activities associated with the completion of the single rising dose study begun in November, 2000 are funded. These charges are expected to be minimal and to be completed by March, 2001.
- BP-414.030 A multiple rising dose and a placebo-controlled Phase IIa trial to evaluate and compare the analgesic properties of ABT-963 to ibuprofen should be blue planned. See attachments for details.

**ABT-594** - (*Attachments B*)

Contact: Mike Biarnesen 8-6514

- G0-143.010 - The project has been funded for M99-114, a Phase II Neuropathic Pain Study (n=275 pts) that started April, 2000, and is projected to end March, 2001.
- BP-143.010 - Milestone funding from July, 2001 forward. Includes preparatory work for End of Phase II meetings projected for October 2001, preparatory work for initiation of Phase III and Phase I studies projected to start 1Q 2002, purchase of additional raw materials to produce the second and third drug substance NDA lots using the Mitsunobu chemistry in step 4, manufacture of Phase III clinical supplies using the 1st NDA lot with Mitsunobu chemistry, etc.

- SPD: process optimization and justification; **proof of principle run at ChemSyn (Mitsunobu route); prepare impurity standards and reference lots; repeat first of three NDA lots using Mitsunobu chemistry in step 4.**
  - PARD: maintain ongoing stability programs; provide clinical supplies for studies; **process optimization; scale-up at AHPI; support SPD process justification; drug substance characterization.**
  - Toxicology: Antigenicity and juvenile rat studies and impurity evaluation.
  - Metabolism: Support human 3H metabolism study.
- **BP-143.014 (ABT-594 Osteoarthritis) - Activities associated with conducting M99-115, a Phase II Osteoarthritis study (n=575 pts), start estimated July, 2001 should be blue planned. See attachments for details.**

**ABT-089 (BP-143.100) - (Attachments C)**

Contact: Mike Biarnesen 8-6514

- **BP-143.100 The following activities are unfunded and should be blue planned. Phase I: first-time-in-man study, single rising dose to start March, 2001 (n=60pts.), and multiple rising dose (n=60pts.) to start July, 2001. Transition Team Go/No Go, November, 2001. PARD, PK, Drug Analysis, and Statistics/Data Management to support Phase I studies identified above. Toxicology to complete activities to support initiation of Phase I studies discussed above, as well as, future (2002) studies in adults and children (male and female) for up to six weeks in duration for Transition team Go/No Go. See attachments.**

**NPS 1776 (BP-121.100) - (Attachments D)**

Contact: Mike Biarnesen 8-6514

- **BP-121.100 The following activities are unfunded and should be blue planned. The completion of pre-clinical stage toxicology and PARD activities. Phase I first-time-in-man study (n=60pts) to start June, 2001; multiple rising dose study (n=60) to start November, 2001; and new formulation study (n=24pts) to start October, 2001. Toxicology and PARD to initiate activities to support initiation of Phase I studies above, including PARD development of controlled-release prototype formulations for human bioavailability studies. PK, Drug Analysis and Statistics/Data Management to support Phase I studies. See attachments for details.**

**ABS-103 / A352086 (BP-121.200) - (Attachments E)**

Contact: Mike Biarnesen 8-6514

- **BP-121.200 The following activities are unfunded and should be blue planned. The completion of pre-clinical stage activities. Phase I first-time-in-man study (n=60pts) to start October, 2001. Toxicology and PARD to initiate activities to support start of Phase I study. See attachments for details.**

**KCO ABT-598 G0-149230 - (Attachments F)**

Contact: Bob Harris 7-9290

Program is approved in 2001 as a transition program. Please contact Bob Harris for any additional details.

**BPII Back-up ABT-980 BP-330000**

Contact: Bob Harris 7-9290

Program was cancelled on October 23, 2000. All closeout activities should be completed in 2000.

**ANTIVIRAL - (Attachments G)**

**Ritonavir ABT-538- (Attachments G)**

Contact: Amy Potthoff 7-1930

**G0-202.133 Complete activities related to SEC filing. No clinical studies.**

**Ritonavir ABT-538 Phase-IV - (Attachments G)**

Contact: Laurel Krause-Hooyman 7-7848

**G0-202.135 Continue M96-462 Long-Term Extension study to July, 2002**

**G0-202.146 Continue Erica A & B clinical programs to December, 2002;**

**Complete NICE study January, 2001.**

**Kaletra ABT-378**

**2nd Generation Protease ABT-378 (with Phase-IV) - (Attachments G)** Contacts: Amy Potthoff 7-1930  
Jeff Drajesk 8-5097

**G0-202.150: NDA approved September 2000. There are several proposed changes to the clinical program. See attachment for details; call Amy Potthoff (registration studies) or Jeff Drajesk (Phase-IV).**

**2nd Generation Protease ABT-378 KNOLL Formulation - (Attachments G)** Contact: Amy Potthoff 7-1930

**G0-202.152: Continuation of the Knoll/Kaletra formulation for 2001. Two Bio studies scheduled for April.**

**HAART Metabolic Complications - (Attachments G)**

Contact: Jeff Drajesk 8-5097

**G0-202.220: Program in metabolic complications of Highly-Active Anti-Retroviral Therapy (HAART) being conducted by Ingenix is supported by a consortium of companies including Abbott.**

**Clarithromycin - (Attachments H)**

Primary Contact: Carol Olson 7-3019

Phase IV Contact: Laurel Hooyman 7-7848

Differentiation - Immunomodulatory (Asthma and Cystic Fibrosis) have been cut to cover only current ongoing studies. All new formulation work has been discontinued. XL for France and Germany has been reduced.

- **Clarithromycin 500 mg Extended Release (G0-206.009) - M99-066, Biaxin XL vs. Augmentin in AECB and M99-077, Biaxin XL vs. Levaquin in CAP have both been completed. The Biaxin XL CAP Step Down and Concomitant Therapy Pilot Study ( M99-083) will complete in 2001.**
- **International Phase IV (G0-206.012) - Support on the International Clarithromycin MR vs. Augmentin in PRSP/DRSP (W99-317) should be budgeted to Project G0-206.012. Support for the proposed Clarithromycin OD XL studies for France and Germany (CAP, AECB, Pharyngitis) should also be budgeted to G0-206.012.**
- **International Formulation Projects - The International 1 Gram Tablet formulation (BP-206.014), the Japan 400mg tablet formulation (BP-206.015), and the International Pediatric Once-A-Day Formulation (BP-206.016) are unfunded in 2001.**
- **Blue Plans - The Tablet and Pediatric Phase IV Bulk Drug (PPD and AI) (BP-206.001 and BP-206.003).**

Ketolide ABT-773 - (Attachments I)

Contact: Carol Meyer 7-4815

- Ketolide ABT-773 - (G0-207.101)  
Phase III studies will be performed in four indications. Six of the ten planned Phase III studies will begin in November, 2000 with the remaining four studies starting in November, 2001. NDA is planned for August, 2002. Scale up activities for the 150mg tablet formulation are based on two manufacturing sites, stability requirements and the filing date.
- Japan Development Plan (G0-207-104) will require repeat of Phase I in Japan. A food effect and dose escalation study will be initiated in 4<sup>th</sup> quarter 2000 to determine the dose for the Phase II/III program. Once Phase I is completed, a meeting with Kiko will be held in May, 2001 to agree on the Phase II/III strategy. Two possible outcomes are currently estimated, either a bridging strategy requiring 2 to 3 Phase II/III studies or full Japanese development requiring 4 -6 Phase II/III studies.
- IV (BP-207.102)  
Pending Phase I results (if funding available) scale-up activities and Phase III step-down therapy studies (Two Studies - US and Europe) will be initiated 4Q 2001.
- Pediatric (BP-207.103)  
Proof of principle PK trial results (2 prototypes vs. tablet) revealed taste and bioequivalency problems. No further development is planned for the two prototype formulations. Formulation strategies for a new pediatric formulation are being reviewed.

Quinolone ABT- 492 (G0-233.270) - (Attachments J)

Contact: Kay Kreutzer 7-3883

- Phase I single rising dose started November, 2000. Fast/Fed/Gender/Elderly study to start January, 2001 followed by multiple dose in February, 2001. Go/No Go decision April, 2001. Three Phase I studies to start 2Q01 with Go/No Go decision in August, 2001. Phase IIA study on AECB comparing ABT-492 (2 doses) to Levoquin to start 3Q01. Phase IIB CAP study to start late 4Q01. Bulk drug, formulation and toxicology needed to support this timeline.
- Quinolone ABT-492 I.V. (BP-233.271) - (Attachments J)  
I.V. formulation effort will begin in January, 2001 pending Blue Plan funding. Assume one manufacturing run in 4Q01. Toxicology pain on injection study and 1month toxicology study on two species.

Neuraminidase ABT-677 (BP-235.010)

Contact: Kay Kreutzer 7-3883

- DDC review was held November 1, 1999 and a decision was made to move the compound to a transition team. Due to the complexity of the chemistry, the transition team decided to proceed on several fronts slowly, rather than concentrate only on the chemistry. This will include chemistry, analytical, toxicology range finding, PK in animals, and outside studies to confirm activity of the drug in new models. Two week toxicology studies to start 2Q 01. A single rising dose study is planned for 3Q01, and a multiple rising dose study for 4Q01.

Cyclosporine - (Attachments L)• Capsule / Liquid Development (G0-249.505)

Contact: Lori Vella-Rountree 7-6304

- AI Liquid Filing: Complete bio study M00-210 using European-Sourced Neoral.
- Marketing studies:
  - M99-033 PK deNovo Liver with LongTerm Extension - to complete December, 2000.
  - M99-041 European Switch Kidney with LongTerm Extension - to complete December, 2001.

- **Phase-IV Co-Promotion (G0-249.506)**

Contact: Jeff Drajesk 8-5097

- Phase-IV preference study M99-133 (PREFER) to complete Q1-2001: number of patients has been reduced to 2200.

**ONCOLOGY-** (Attachments M)

Contacts: Robert Hansen 7-9418 & John Groff 7-2594

**Oncology Funded programs:**

- **Endothelin ABT-627 (G0-631.300)**  
2001 Plan funding should reflect dosing for two Phase III pivotal trials (M00-211 and M00-244) plus a long-term extension (M00-258), four drug interaction studies (Fexofenadine, Midazolam, Ketoconazole and Rifampin), a definitive QTc biosafety study and a food effects/bio-equivalency study. All other indications associated with Endothelin (ABT-627) should be Blue Planned.
- **MMPI #2 ABT-518 G0-631.221**  
M00-235 Multiple Escalating Dose in 40 patients to begin February, 2001.  
Initiate an IND Study June, 2001 with 14 patients.
- **TSP #1 ABT-510 G0-631.240**  
M99-106 Single Dose in 43 subjects with final group dosed 11/2/00.  
M00-153 Multiple Dose with Long Term Extension in 80 patients to begin January, 2001.  
Initiate an IND study June, 2001 with 14 patients.
- **Anti-Mitotic ABT-751 G0-631.282**  
M00-231 MTD scheduled to initiate April, 2001 with 40 patients.  
IND Study scheduled to initiate June, 2001 with 24 patients.  
Phase II scheduled to initiate in the following manner: two 30 patient studies in November, 2001 and two 30 patient studies in December, 2001.

**Oncology Blue Plan:**

- **TSP #2 BP-631.242** - DDC delayed to 1Q/01.  
Assuming successful 4Q/2001 DDC, then preclinical support up to but not including Phase I.
- **K5 ABT-828 BP-631.241**  
Delivery of Drug Substance in October, 2001.
- **FTI #2 BP-631.204**  
Assuming successful 2Q/2001 DDC, then initiate Phase I 1Q/02.
- **Endothelin ABT-627 BP-631.305**  
Eight additional Phase II trials (40 patients each) in Prostate Cancer [a) Bisphosphonate and b) Taxane Combinations] and other cancers [c) Ovarian, d) Brain, e) Colorectal, f) Renal, g) Breast and h) Cervical].

**Bimoclomol ABT-822 - (Attachments N)**

Contact: Pat Harrigan 7-7346

- **BP-632.120 - Base Program:** Two Phase-III studies (Europe and US) to be initiated September 2001, with 1200 patients each at 100 sites each for registration.
- **BP-632.122** - Initiate Toxicology studies: 2-year carc in rats (March, 2001), 3-month MTD in Tg. AC mice (March, 2001) and 6-month carc in Tg. AC mice (September, 2001).
- **BP-632.124** - Initiate CYP 2D6 Interaction June, 2001. Metabolism initiative TBD.
  - **BP-632.125** - Complete initiate formulation Development (March, 2001), prepare Phase-III clinical supplies (June, 2001) and initiate commercial formulation development (July 2001).

**PPD DEVELOPMENT (DOMESTIC):**

**Pharmacogenetics**

Contact: Brian Spear 7-5437 or Diane Barnes 7-2434

- Genset program is unfunded.
- For specific clinical studies requiring DNA sampling, the sample collection and central lab storage costs (approx. \$31 per patient) is to be included in Venture study grants; cost for subsequent transfer and retention at Abbott Park will be absorbed by Pharmacogenetics.

**Depakote - (Attachments O)**

Contact: Greg Lenz 5-0875

Ongoing Depakote studies:

- Elderly Agitation (P1-122.042) M99-082.
- Impulsive Aggression (P1-121.035) M99-002.
- Psychosis (P1-121-038) M99-010.
- Dose Proportionality (P1-121.009) M00-232 completed November 2000 at ACPRU; reports only.

New study Initiations:

- Depakote Polycystic Ovary - PCO (P1-121.046) – outside study grant; no in-house support

Unfunded Programs:

- Dose Proportionality Repeat (BP-121.009) **July 2001 pending FDA review.**
- Depacon Acute Migraine (BP-121.031) **July 2001.**
- Depakote DR/ER Switch in Bipolar (BP-121.049) **July 2001.**
- Depacon Status Epilepticus (BP-121.047) **September 2001.**
- New 250mg ER Tablet formulation (BP-121.043) **TBD.**
- Depakote 250mg Sprinkle Capsule formulation development (BP-121.050) **TBD.**
- Depakote DR Smaller Tablet formulation development (BP-121.045) **TBD.**
- ER Adolescent PK (BP-121.048) **August 2001 to support FDA Pediatric-Use rule.**
- Depakote Pediatric Psychiatry (BP-121.041) **January 2002.**
- 

**Gabitril**

Contact: Greg Lenz 5-0875

- Program discontinued.

**Fenofibrate ABT-799 -**

Contact: Daniel Yannicelli 5-1280

- Program is unfunded.

**Omnicef (P1-241.100) - (Attachments R)**

Contact: Carol Olson 7-3019 / Laurel Hooyman 7-784

- One Phase IV study in Otitis Media is planned to be initiated 3Q 2001 vs. Zithromax.

**NEW DEVELOPMENT CANDIDATES:**

Unfunded in the 2001 Plan.

**OTHER PROJECTS NOT FUNDED**

- Alternate Dosage
- In-licensing
- Exploratory Effort
- Prescription for Growth
- R-UK

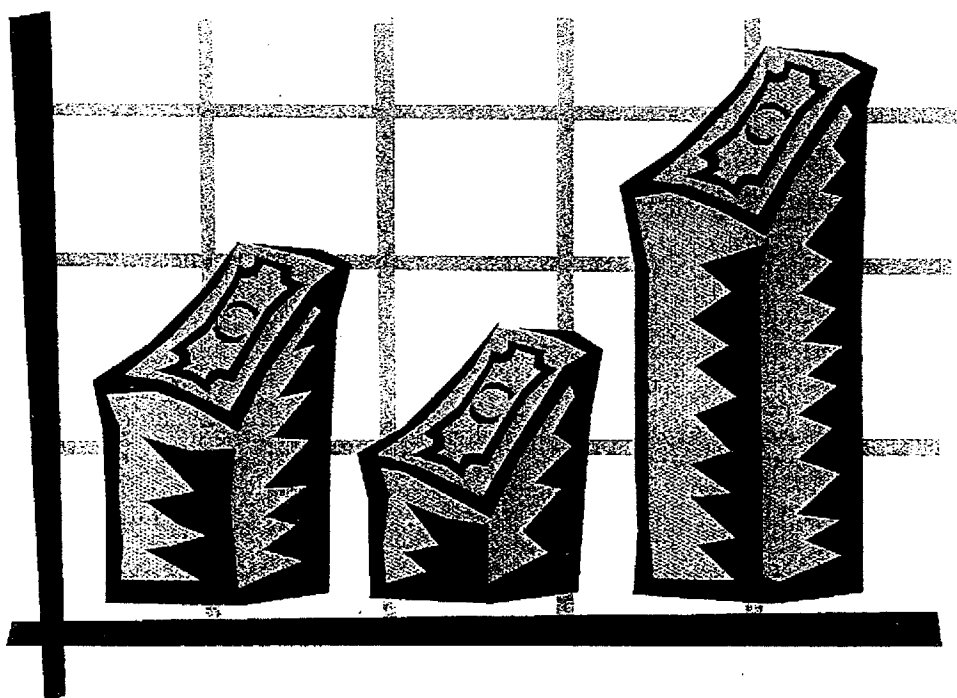




# **PORTFOLIO ANALYSIS**

**JANUARY  
2001  
REVIEW**

**REFERENCE  
MATERIALS**



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ABBT 0012369

**PORTFOLIO  
ANALYSIS**

**JANUARY**

**2001**

**REVIEW**

**REFERENCE**

**MATERIALS**

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ABBT 0012370

Pharmaceutical Portfolio Analysis

2001 APU Kick-off Meeting

January 29, 2001

Agenda

- Portfolio Analysis Overview & Goals of Meeting
- Data Gathering Process
- Data Analysis
  - Review Key Summary Materials
- Portfolio Optimization
  - Evaluation of 2001 Plan
  - “Roadmap” vs 2001 Plan
- Prioritize Blue Plan projects

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***Goal of Portfolio Analysis:***

- Identify the Portfolio of Pharmaceutical R&D projects that enables Abbott to achieve its business goals.

***Goal of Today's Meeting:***

- Review 2001 Plan funding assumptions – opportunity to reprioritize for April Update
- Outline Blue Plan priorities

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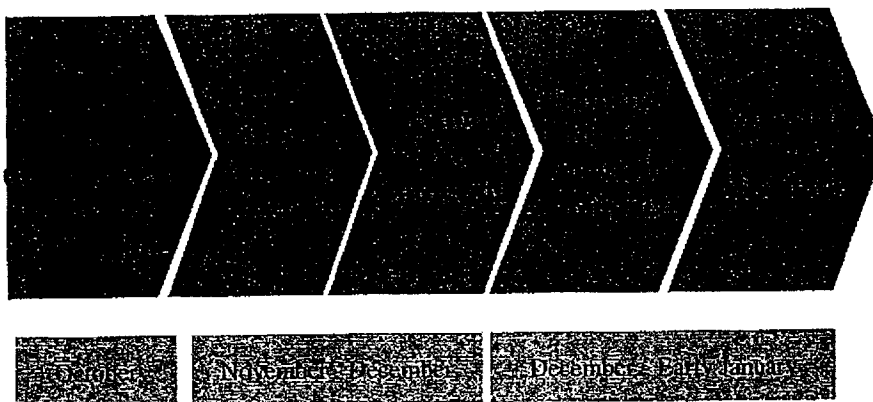
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### Portfolio Analysis Data Gathering Process Improvements

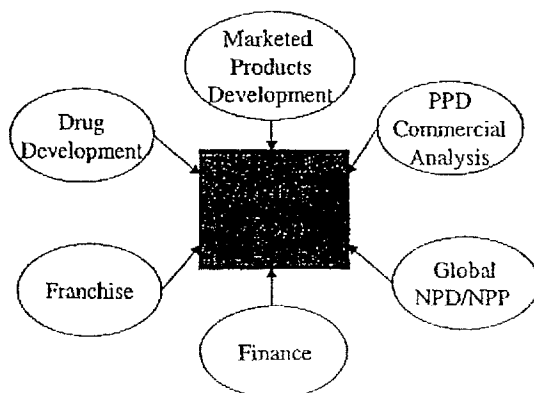
- Quality of the Portfolio Data significantly upgraded from July 2000 Analysis
- How did we do this?
  - Project Teams formed
  - DSG Facilitated Working Sessions
  - Internal Project Reviews
  - Commercial and Technical Risk assumptions documented

### Data Gathering Process



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### ***DATA GATHERING: A Global, Cross-Functional Initiative***



#### 2001 Project Teams

- ABT-773
- ABT-492 & ABT-677
- Clari & Omnicef
- HIV
- Tricor
- Gengraf
- Neurology Development
- Depakote
- Oncology
- Urology (KCO)

#### Project Teams: Roles & Responsibilities

Each project team is composed of the following:

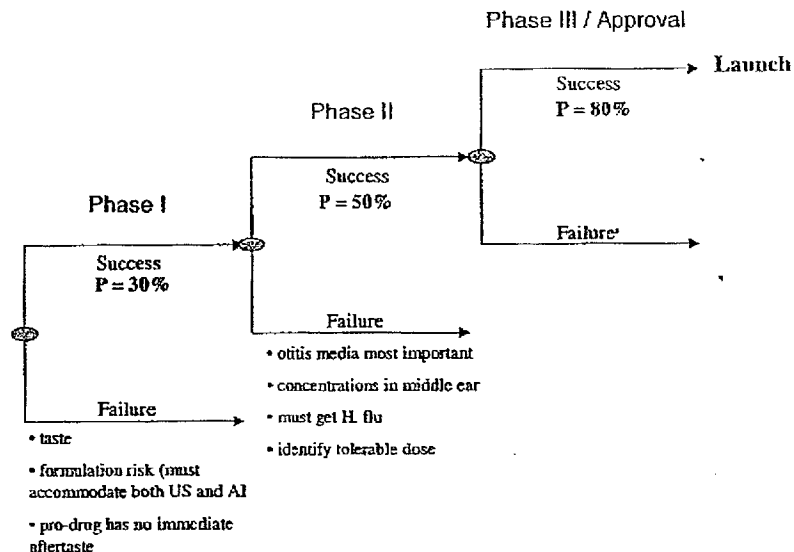
Team Member	Role/Responsibilities
Venture Head / Mktd Prod Head / Franchise Head	Ultimately responsible for quality of final submission to portfolio
Medical Director	Major contributor to product profile discussion
Operations Manager	Oversees team's progress. Calculates R&D costs
PPD NPD Mgr / Commercial Analysis Mgr	Domestic commercial forecasts & product profile definitions
AI NPD Mgr / Business Development Mgr	International commercial forecasts & product profile definitions
R&D Financial Analyst	Assist Ops Mgr in calculating R&D costs
DSG Analyst	Facilitate information gathering/decision meetings.

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### Project Team Working Sessions

- Goal of working session was to define:
  - List of projects including definition
  - Product “profile” assuming successful project outcome
  - Success probabilities for each phase of development and assessment rationale
- DSG facilitated working sessions to promote a consistent, structured approach toward gathering portfolio data
- Feedback from teams is that this process has been very effective. Dramatically improves communication and facilitates strategy development and teamwork across functions/divisions.

### Project: ABT-773 Pediatric Form



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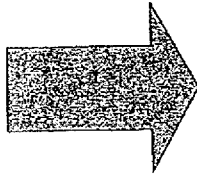
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ABT- 773		Intel - B308	
<b>Project Information</b> Project Name: <u>Abt-773 (R-773)</u> Project Phase: <u>ABT-773 (R-773)</u> Abbreviated Project Title: <u>ABT-773</u> Project Start: <u>1968</u> Project End: <u>1972</u> Project Duration: <u>4</u> years Project Status: <u>Completed</u>			
<b>Developmental Timeline</b> Activities: <u>Phase 1</u> Phase 2 Phase 3 Phase 4 Phase 5 Phase 6 Phase 7 Phase 8 Phase 9 Phase 10 Phase 11 Phase 12 Phase 13 Phase 14 Phase 15 Phase 16 Phase 17 Phase 18 Phase 19 Phase 20 Phase 21 Phase 22 Phase 23 Phase 24 Phase 25 Phase 26 Phase 27 Phase 28 Phase 29 Phase 30 Phase 31 Phase 32 Phase 33 Phase 34 Phase 35 Phase 36 Phase 37 Phase 38 Phase 39 Phase 40 Phase 41 Phase 42 Phase 43 Phase 44 Phase 45 Phase 46 Phase 47 Phase 48 Phase 49 Phase 50 Phase 51 Phase 52 Phase 53 Phase 54 Phase 55 Phase 56 Phase 57 Phase 58 Phase 59 Phase 60 Phase 61 Phase 62 Phase 63 Phase 64 Phase 65 Phase 66 Phase 67 Phase 68 Phase 69 Phase 70 Phase 71 Phase 72 Phase 73 Phase 74 Phase 75 Phase 76 Phase 77 Phase 78 Phase 79 Phase 80 Phase 81 Phase 82 Phase 83 Phase 84 Phase 85 Phase 86 Phase 87 Phase 88 Phase 89 Phase 90 Phase 91 Phase 92 Phase 93 Phase 94 Phase 95 Phase 96 Phase 97 Phase 98 Phase 99 Phase 100 Phase 101 Phase 102 Phase 103 Phase 104 Phase 105 Phase 106 Phase 107 Phase 108 Phase 109 Phase 110 Phase 111 Phase 112 Phase 113 Phase 114 Phase 115 Phase 116 Phase 117 Phase 118 Phase 119 Phase 120 Phase 121 Phase 122 Phase 123 Phase 124 Phase 125 Phase 126 Phase 127 Phase 128 Phase 129 Phase 130 Phase 131 Phase 132 Phase 133 Phase 134 Phase 135 Phase 136 Phase 137 Phase 138 Phase 139 Phase 140 Phase 141 Phase 142 Phase 143 Phase 144 Phase 145 Phase 146 Phase 147 Phase 148 Phase 149 Phase 150 Phase 151 Phase 152 Phase 153 Phase 154 Phase 155 Phase 156 Phase 157 Phase 158 Phase 159 Phase 160 Phase 161 Phase 162 Phase 163 Phase 164 Phase 165 Phase 166 Phase 167 Phase 168 Phase 169 Phase 170 Phase 171 Phase 172 Phase 173 Phase 174 Phase 175 Phase 176 Phase 177 Phase 178 Phase 179 Phase 180 Phase 181 Phase 182 Phase 183 Phase 184 Phase 185 Phase 186 Phase 187 Phase 188 Phase 189 Phase 190 Phase 191 Phase 192 Phase 193 Phase 194 Phase 195 Phase 196 Phase 197 Phase 198 Phase 199 Phase 200 Phase 201 Phase 202 Phase 203 Phase 204 Phase 205 Phase 206 Phase 207 Phase 208 Phase 209 Phase 210 Phase 211 Phase 212 Phase 213 Phase 214 Phase 215 Phase 216 Phase 217 Phase 218 Phase 219 Phase 220 Phase 221 Phase 222 Phase 223 Phase 224 Phase 225 Phase 226 Phase 227 Phase 228 Phase 229 Phase 230 Phase 231 Phase 232 Phase 233 Phase 234 Phase 235 Phase 236 Phase 237 Phase 238 Phase 239 Phase 240 Phase 241 Phase 242 Phase 243 Phase 244 Phase 245 Phase 246 Phase 247 Phase 248 Phase 249 Phase 250 Phase 251 Phase 252 Phase 253 Phase 254 Phase 255 Phase 256 Phase 257 Phase 258 Phase 259 Phase 260 Phase 261 Phase 262 Phase 263 Phase 264 Phase 265 Phase 266 Phase 267 Phase 268 Phase 269 Phase 270 Phase 271 Phase 272 Phase 273 Phase 274 Phase 275 Phase 276 Phase 277 Phase 278 Phase 279 Phase 280 Phase 281 Phase 282 Phase 283 Phase 284 Phase 285 Phase 286 Phase 287 Phase 288 Phase 289 Phase 290 Phase 291 Phase 292 Phase 293 Phase 294 Phase 295 Phase 296 Phase 297 Phase 298 Phase 299 Phase 300 Phase 301 Phase 302 Phase 303 Phase 304 Phase 305 Phase 306 Phase 307 Phase 308 Phase 309 Phase 310 Phase 311 Phase 312 Phase 313 Phase 314 Phase 315 Phase 316 Phase 317 Phase 318 Phase 319 Phase 320 Phase 321 Phase 322 Phase 323 Phase 324 Phase 325 Phase 326 Phase 327 Phase 328 Phase 329 Phase 330 Phase 331 Phase 332 Phase 333 Phase 334 Phase 335 Phase 336 Phase 337 Phase 338 Phase 339 Phase 340 Phase 341 Phase 342 Phase 343 Phase 344 Phase 345 Phase 346 Phase 347 Phase 348 Phase 349 Phase 350 Phase 351 Phase 352 Phase 353 Phase 354 Phase 355 Phase 356 Phase 357 Phase 358 Phase 359 Phase 360 Phase 361 Phase 362 Phase 363 Phase 364 Phase 365 Phase 366 Phase 367 Phase 368 Phase 369 Phase 370 Phase 371 Phase 372 Phase 373 Phase 374 Phase 375 Phase 376 Phase 377 Phase 378 Phase 379 Phase 380 Phase 381 Phase 382 Phase 383 Phase 384 Phase 385 Phase 386 Phase 387 Phase 388 Phase 389 Phase 390 Phase 391 Phase 392 Phase 393 Phase 394 Phase 395 Phase 396 Phase 397 Phase 398 Phase 399 Phase 400 Phase 401 Phase 402 Phase 403 Phase 404 Phase 405 Phase 406 Phase 407 Phase 408 Phase 409 Phase 410 Phase 411 Phase 412 Phase 413 Phase 414 Phase 415 Phase 416 Phase 417 Phase 418 Phase 419 Phase 420 Phase 421 Phase 422 Phase 423 Phase 424 Phase 425 Phase 426 Phase 427 Phase 428 Phase 429 Phase 430 Phase 431 Phase 432 Phase 433 Phase 434 Phase 435 Phase 436 Phase 437 Phase			

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How do we "value" the projects?Project Team Inputs

- 15 year global P&L
  - Base Case
  - Upside
  - Downside
- Technical success probabilities for each phase of development
- Development timeline
- R&D expense by year
- Documented Assumptions

Project "Value Measures"

- Expected Value
- Short Term Revenue Contribution
- Long Term Profit Contribution
- R&D Productivity Index

**Value Measure Calculations**

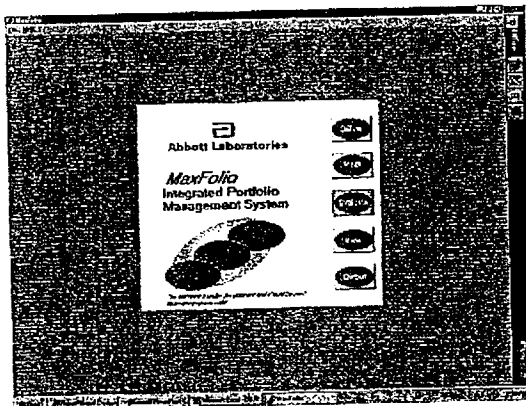
Expected Value (EV)	NPV Division Margin adjusted for Risk (Incorporates technical and commercial risk including all three forecasts: Base, Upside, Downside)
Short Term Revenue Contribution	2003 - 2006 Base Case Sales
Long Term Profit Contribution	2007 - 2011 Base Case Division Margin
Productivity Index (PI)	EV / NPV R&D (Primarily used for valuing Mktd Product projects due to smaller R&D investment requirements)

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### Internal Reviews

- Goal of the Internal Projects Reviews was to:
  - Review Value Measures & Rankings within Franchise
  - Confirm all key data
    - project assumptions
    - technical success probabilities
    - commercial forecasts
    - R&D expenses
  - Promote "ownership" of data by team
- The project teams' final proposals are published in the reference materials binder.

### ANALYSIS: Database Functionality



- MaxFolio software enables us to identify the portfolio that will optimize one or several "value measures"
- We can analyze data by:
  - Entire portfolio
  - Franchise
  - Phase
  - Risk level
  - Custom portfolios

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### 2001 Budget Calculation

			<u>Variance</u>	
	July 2000 Funding Assumptions	January 2001 Funding Assumptions	\$	%
Total R&D Budget	630	572	(58)	-9%
Less: Discovery	(200)	(192)	8	-4%
Less: Other	<u>(50)</u>	<u>(96)</u>	<u>(36)</u>	60%
2001 Development Budget	<u>370</u>	<u>284</u>	<u>(86)</u>	-23%
Plus: Incremental Blue Plan Funding	50	100	50	100%
2001 Development Budget + Blue Plan	<u>420</u>	<u>384</u>	<u>(36)</u>	-9%

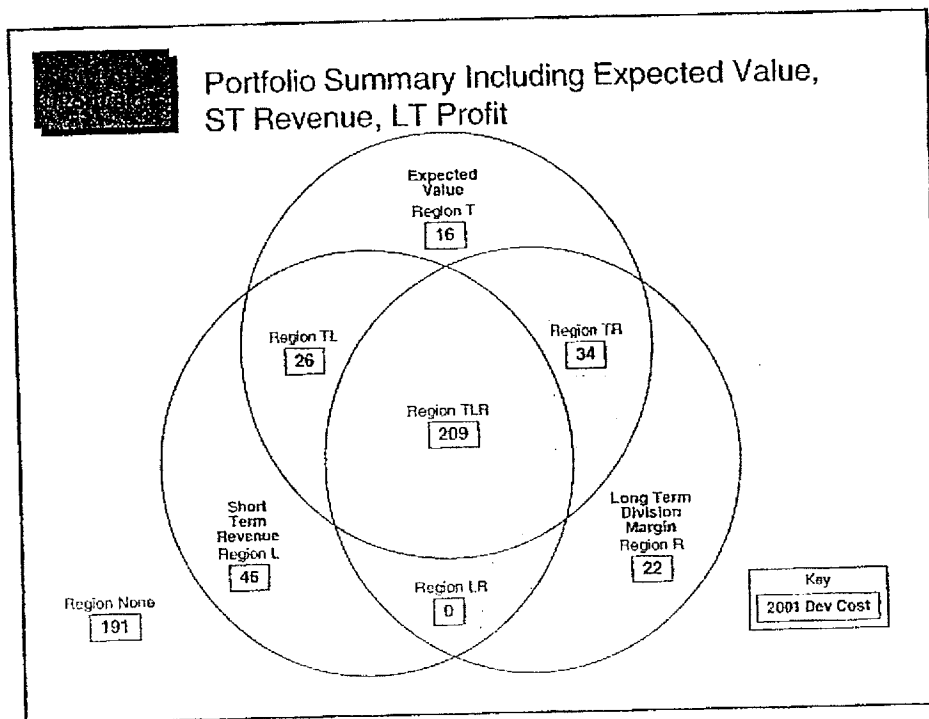
Value Measure Summary - Sorted by Expected Value (I)

Category	Program	Program Description	Fiscal Year of Budget	Estimated FY1995 Expenditure	FY95 Reduction (in \$ mil.)	FY95 Reduction (%)	Estimated FY1995 Expenditure	Estimated FY1995 Expenditure	Estimated FY1995 Expenditure	Estimated FY1995 Expenditure	Estimated FY1995 Expenditure	Estimated FY1995 Expenditure
Medical	Cancer	Cow Program: HIV, HD, DNAL	95%	2463.0	2362.7	204.9	51.8	38.3	22.8			
Medical	ABIS-100AB-1776	Epilepsy, Migraine, Elderly	28%	536.2	0.0	264.9	3.8	72.1	44.8			
Medical	ABIS-127 (Gastro)B	Prostate Cancer 2 Clinical Trials	75%	276.5	274.5	1294.6	4.3	42.0	96.9			
Medical	ABIS-773 (Kidney)	Heart	72%	316.5	900.9	1471.2	2.5	87.0	173.3			
Medical	ABIS-773 (Kidney)	Heart Pain	32%	386.1	433.9	2127.1	5.5	17.9	191.1			
Medical	ABIS-394	Soft Tumor Cancer	29%	234.9	72.0	1369.9	3.8	12.0	204.1			
Medical	ABIS-510 (ISP-II)	Pain and Osteo	38%	238.9	62.5	1065.5	3.7	2.0	206.1			
Medical	ABIS-943 (COX)	Early Stage Pca Patients	55%	183.5	12.3	531.2	4.0	11.0	217.1			
Medical	ABIS-527 (Endocrine)	Rehabilitation Analog	22%	163.5	488.2	1629.9	3.7	15.0	232.1			
Medical	VM 329	Soft Tumor Cancer	22%	158.3	0.0	589.5	3.7	10.0	226.1			
Medical	ISP-2	New Formulations	16%	142.1	130.0	2001.1	2.1	2.2	234.5			
Medical	Degenerative	Peds ER Patient Extn - Psychiatry	95%	129.0	0.0	345.0	28.0	8.9	235.0			
Medical	Degenerative	Peds ER Patient Extn - Psychiatry	90%	139.5	480.0	223.0	57.3	1.5	235.9			
Medical	Freebone	Pd Women	75%	124.4	388.0	253.9	14.9	1.5	297.4			
Medical	Degenerative	Cerebral: ER Adult Male	31%	119.4	48.5	771.6	2.1	10.0	247.2			
Medical	ABIS-151 (Anti-Melan)	Soft Tumor Cancer	95%	107.0	28.4	34.0	15.0	6.9	254.7			
Medical	Trans	Expanded Access	90%	104.2	171.5	230.0	67.8	8.4	225.7			
Medical	Cachexia	Clinical Trials: Efficacy/Toxicity	90%	104.2	171.5	230.0	67.8	8.4	225.7			
Medical	ABIS-727 (Anti-Melan)	New Proteinase Cancer	48%	98.7	24.7	342.2	5.9	2.0	258.4			

Sorts by ST Revenue, LT Profit and Productivity Index are also included in the Summary Section

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**Portfolio Summary Including Expected Value, ST Revenue, LT Profit Listing (I)**

Region	Therapeutic	Program	Project	Expected Value (\$ millions)	ST Revenue (\$ millions)	Long Term Division Margin (\$ millions)	Net Cost (\$ millions)
TLR	One	ABT-510 (TSP-1)	Solid Tumor Cancer	234.9	72.0	130.9	12.0
TLR	Neuro	ABT-594	Chronic Persistent Pain	80.1	119.8	713.8	3.2
TLR	Neuro	ABT-594	Neuro Pain	380.7	433.9	2127.1	17.2
TLR	One	ABT-627 (Endothelin)	Prostate Cancer 2 Clinical Trials	570.6	274.5	1294.5	42.0
TLR	Anti-Infect	ABT-773 (Ketofido)	Tablet	521.5	900.9	1471.2	87.0
TLR	HIV/Trans	Kaletra	Core Program: HIV; BID, ORAL	2481.0	2302.7	2104.8	32.8
TLR	One	YH 529	Bisphosphonate Analog	161.5	468.2	1628.8	15.0
TLR	Neuro	ABT-103/MP-5-1778	Epilepsy, Migraine, Bipolar	585.2	0.0	2094.8	12.1
TR	One	ABT-751 (Anti-Mitotic)	Solid Tumor Cancer	119.4	45.6	771.8	10.0
TR	One	ABT-828 (K2)	Solid Tumor Cancer	90.5	0.0	808.9	8.8
TR	Neuro	ABT-953 (COX4)	Pain and Osteo	233.9	63.5	1006.8	3.0
TL	Anti-Infect	Clarithromycin	Clari Market Enhancement	104.2	171.5	250.8	0.4
TL	Neuro	Depakote	Depakote ER Adult Male	124.4	258.0	253.8	1.3
TL	Neuro	Depakote	New Formulations	142.9	130.0	200.1	2.2
TL	Uro/Cardio	Fenofibrate	Pain Statin Reformation RTP	85.8	718.0	148.8	4.5
TL	Uro/Cardio	Fenofibrate	PM Women	129.5	460.0	328.0	1.5
TL	HIV/Trans	Kaletra	Expanded Access	107.9	88.4	34.0	8.9
TL	HIV/Trans	Kaletra	Knoll Reformation	81.7	85.0	224.8	2.0
TL	HIV/Trans	Kaletra	Phase IV Switch	78.4	72.0	21.7	6.0
T	One	ABT-627 (Endothelin)	Combination Bisphosphonates	93.9	27.2	234.6	1.0
T	One	ABT-627 (Endothelin)	Early Stage Pca Patients	133.5	12.3	531.2	11.0
T	One	ABT-627 (Endothelin)	Non Prostate Cancer	98.7	24.7	342.2	3.0
T	Neuro	Depakote	Peds ER Patient Extn - Psychiatry	129.8	0.0	345.0	0.8
T	One	TSP-2	Solid Tumor Cancer	158.9	0.0	563.5	0.0
R	One	ABT-518 (MMP3)	Solid Tumor Cancer	48.3	21.6	707.8	9.0
R	Uro/Cardio	ABT-822 (Bisphosphonate)	Diabetic Neuropathy	40.0	68.0	986.5	13.4
L	Anti-Infect	ABT-492 (Cefuroxime)	Tablet	33.9	53.9	648.3	23.5

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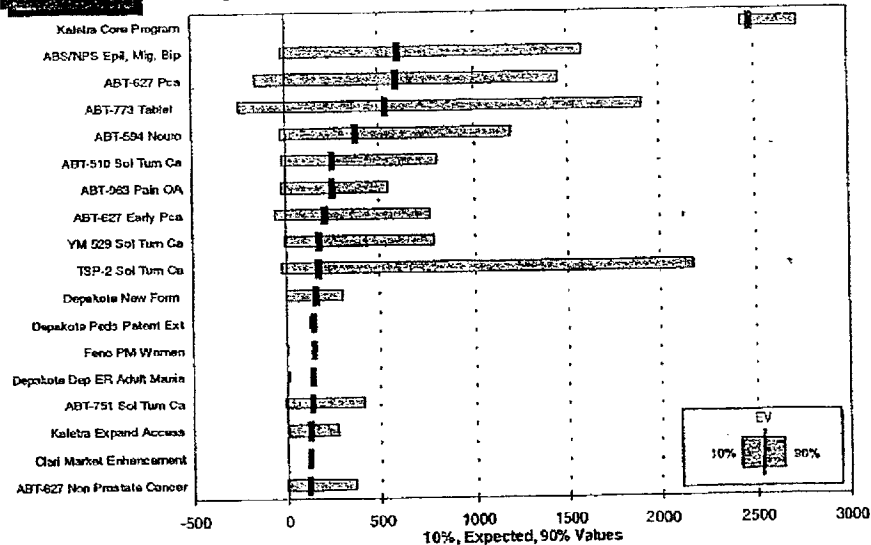
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### Top 10 Value Measure Summary - Sorted by Expected Value (I)

Therapeutic Area	Program	Project	Probability of Success (%)	Expected Value (\$M)	Short-Term Revenue Rank	Long-Term Division Margin Rank	Productivity Index Rank	Next Year Cost (\$M)	Next Year Sales (\$M)
HN/Thera	Kaletra	Core Program: HIV, BID, DRAL	95%	1	1	2	4	37.6	32.3
Neuro	ABS-103/NPS-3776	Epilepsy, Migraine, Bipolar	38%	2	75	3	53	12.1	44.8
Onc	ABT-527 (Endothelin)	Prostate Cancer 2 Clinical Trials	75%	3	8	7	47	42.0	85.5
Anti-Infect	ABT-773 (Kaletra)	Tablets	72%	4	2	5	64	87.0	173.9
Neuro	ABT-594	Neuro Pain	32%	5	5	1	44	17.2	151.1
Onc	ABT-510 (TSP-1)	Solid Tumor Cancer	29%	5	26	6	54	12.0	203.1
Neuro	ABT-963 (COX-1)	Pain and Osteo	35%	7	33	8	55	3.0	206.1
Onc	ABT-627 (Endothelin)	Early Stage Pca Patients	55%	8	63	37	50	11.9	217.1
Onc	YM 529	Bisphosphonate Analog	22%	9	4	4	56	15.0	232.1
Onc	TSP-2	Solid Tumor Cancer	72%	10	75	18	59	0.0	238.1
Uro/Cardio	Feno/Bralo	PM Women	82%	13	5	24	3	1.5	233.8
Neuro	Depakote	Depakote ER Adult Mania	75%	14	7	26	25	1.3	234.9
Anti-Infect	Cladribine	Cladribine Enhancement	90%	17	11	77	1	0.4	235.0
Onc	ABT-523 (K5)	Solid Tumor Cancer	21%	20	75	10	70	6.8	244.1
Uro/Cardio	Feno/Bralo	Feno Statin Combination R1P	75%	21	5	34	32	4.5	248.5
Neuro	Depakote	Dose Proportionality	90%	26	19	49	7	2.0	250.8
Uro/Cardio	Feno/Bralo	Diabetic	80%	28	9	32	17	1.1	251.7
Uro/Cardio	Feno/Bralo	Feno Statin Combination Combo	75%	29	10	20	45	2.1	253.0

### Project EV (80% Confidence Interval) (I)



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2001 Analysis: Key Messages

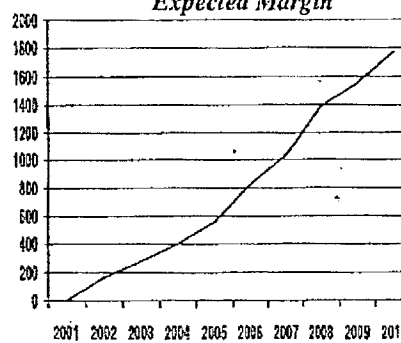
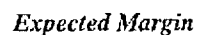
- Confirmed top 4 projects: ABT-773, Kaletra, ABT-627 & ABT-594 (same results as July 2000 analysis)
- YM 529 ranked very high – oncology team stressed that additional due diligence is still needed on this compound and in-licensing deal is not final.
- ABT-677 (Neuraminidase) is the least attractive development project in portfolio.
- Phase IV projects most effectively measured by Productivity Index rather than Expected Value since investment and return are smaller than development projects.

Portfolio Optimization

- Funding Scenarios
  - 2001 Plan Funding Assumptions
  - Prioritization based on Key Value Measures
    - Expected Value
    - Short Term Revenues
    - Long Term Profit
    - Productivity Index
  - “Roadmap” – hybrid of EV & PI

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	—2001 Plan						—2001 Plan			
2001 Plan Expected Sales & Margin	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Sales	266	544	745	993	1,239	1,568	1,888	2,357	2,490	2,735
Margin	(35)	160	280	400	555	823	1,032	1,388	1,551	1,772



## January 2001 Prioritization Meeting Funding Strategies

Function	Project Name	2001 PMN	Current Funding Request	Funding Strategies					Productivity Index	"Road Map"
				Expected Value	ST Revenue	LT Profit				
Neurosurgery	Curative	24.1	35.3	132	20.1	2.9		36.3	28.7	
	Curative									
	Curative	5.5	20.4	20.4	20.4	20.4	20.4	20.4	20.4	20.4
	Curative	1.2	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
	Curative	0.7	7.0							
	Curative	0.5	12.1	12.1				12.1	12.1	12.1
	Curative	0.5	12.1	12.1				1.5		
	Curative	4.0	4.0							
	Curative	39.5	39.5	48.7	42.3	44.2	44.2	72.8	66.3	
	Curative	14.8	23.7	3.3	6.6	1.8		22.3	5.6	
Auto-Infective	Curative	4.0	13.2							
	Curative	81.0	98.5	110.0	55.5	88.0		19.4		69.0
	Curative	24.5	59.4							
	Curative		37.2							
	Curative	122.2	237.4	88.2	128.5	109.3		22.3	93.6	
	Curative	2.3		2.3	2.3	2.3		2.3	2.3	2.3
	Curative	1.4	11.2	7.6	10.8	1.8		10.8	9.1	
	Curative		13.4					13.4	13.4	
	Curative	5.0	4.5		13.1	17.3		24.3	11.8	
	Curative	8.7	29.7	9.9	2.0	2.0		7.7	2.9	
HIV/Transplant	Curative	4.0	4.1	2.0				99.8	57.5	
	Curative	68.8	69.8	48.5	49.5	32.8		2.8	1.2	
	Curative	2.5	7.9		0.9			80.1	62.1	
	Curative	57.5	80.5	50.5	52.5	42.0		58.0	47.0	
	Curative	35.8	38.0	57.0	42.0					
	Curative	7.4	9.0							
	Curative	10.0	12.0	12.0	12.0	12.0		12.0	12.0	12.0
	Curative	8.4	10.0	10.0				8.0	5.1	
	Curative		8.3	8.5						
	Curative		4.1							
Oncology	Curative		15.0	15.0	15.0	15.0		15.0	15.0	15.0
	Curative	64.8	112.8	102.8	69.9	56.8		100.1	21.7	
	Curative		20.8							
	Curative									
	Curative									
	Curative									
	Curative									
	Curative									
	Curative									
	Curative									
Diet	Curative	119.3	118.3	118.3	118.3	118.3		118.3	118.3	118.3
	Curative	284.3	549.0	283.3	285.1	284.3		284.3	284.3	284.3
Total										

APU Budget Assumption \$ 284.3

"Roadmap" Methodology

- **Step 1:** Fund all projects meeting all 3 Value Measures:
  - Expected Value, ST Revenue, LT Profit
  - Included BPH since these are shut down costs.
- **Step 2:** Fund Phase IV projects using 2001 Plan budget allocation (\$102MM including Kaletra).
  - Phase IV prioritized using Productivity Index
  - Funded all "Ph IV Commitments" projects since these represent fixed costs
- **Step 3:** Fund projects meeting at least 2 of 3 value measures with highest EV

Same methodology used in the July 2000 Prioritization Meeting

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## January 2001 Prioritization Meeting "Roadmap"

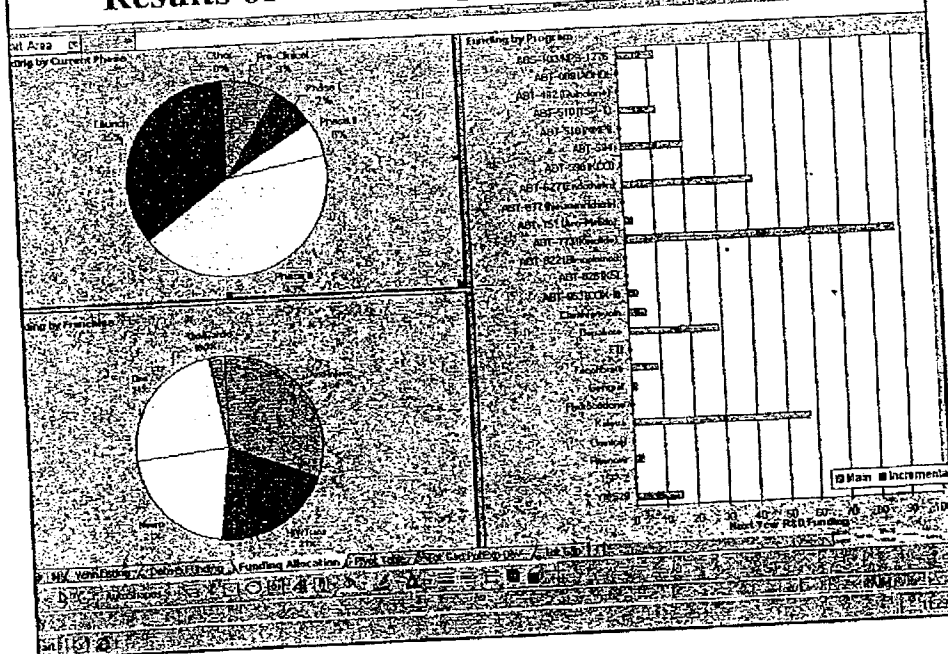
Priority	Program Name	2001 Plan	Current Funding Requests	Prioritization Roadmap			Total
				Project Meeting All Three Value Measures	Phase IV Projects - based on PI	Project Meeting 2 of 3 Value Measures	
Neuroscience	Basaloid	23.1	28.3				28.7
	Subtotal						
	ABT-100	8.9	20.4	20.4			20.4
	ABT-101	3.2	3.8				3.8
	ABT-102	0.7	7.6				7.6
Anti-Infective	ABT-103	0.1	12.1				12.1
	ABT-104	4.0	4.0				4.0
	ABT-105	4.0	4.0				4.0
	ABT-106	4.0	4.0				4.0
	ABT-107	4.0	4.0				4.0
Virology/Cardiology	Subtotal - Neuroscience	35.3	62.8	20.4	20.7	15.7	66.2
	Subtotal - Anti-Infective	14.9	25.7		6.8		25.8
	Subtotal - Virology/Cardiology	4.0	15.3				15.3
	Subtotal - HIV/Transplant	18.0	22.5	22.5			22.5
	Subtotal - Oncology	24.5	37.2				37.2
HIV/Transplant	ABT-108	13.3	23.4	23.4	5.1		28.5
	ABT-109	2.3	2.3				2.3
	ABT-110	1.4	1.4				1.4
	ABT-111	1.4	1.4				1.4
	ABT-112	1.4	1.4				1.4
Oncology	Subtotal - HIV/Transplant	5.9	13.4				13.4
	Subtotal - Oncology	5.1	26.7	2.3			29.0
	Subtotal - HIV/Transplant	4.0	8.1				8.1
	Subtotal - Oncology	51.0	69.6	32.8	24.7	1.7	110.2
	Subtotal - HIV/Transplant	2.3	2.3				2.3
Other	ABT-113	57.8	10.2	10.2	29.3		97.3
	ABT-114	30.8	18.0	18.0			48.8
	ABT-115	7.4	8.0				15.4
	ABT-116	19.0	12.0	12.0			31.0
	ABT-117	8.4	10.0				18.4
Total	ABT-118		8.4				8.4
	ABT-119		15.0	15.0			30.0
	ABT-120		110.0	110.0			220.0
	ABT-121		20.0				20.0
	ABT-122		11.3	11.3			22.6
Total	ABT-123		194.2	194.2	72.3	17.8	384.3
	ABT-124		549.0	549.0			1098.0
	ABT-125		11.3	11.3			22.6
	ABT-126		194.2	194.2	72.3	17.8	384.3
	ABT-127		11.3	11.3			22.6

APU Budget Assumption 5 284.3

Cumulative Funding Amount

Budget Remaining

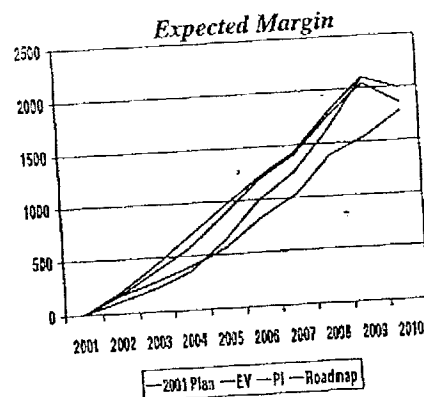
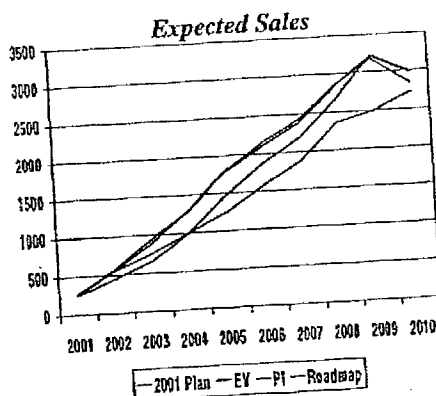
## Results of "Roadmap" Funding Scenario



### 2001 Analysis: Optimization Key Message

- A Reprioritization of 2001 Plan could yield over \$500MM incremental sales in years 2005 and beyond. Requires
  - Incremental investment in Neurology and Oncology
  - Lower investment in Anti-Infective projects

### **Funding Strategy Impact on Global Sales & Margin**



Variance: Roadmap vs 2001 Plan									
	2001	2002	2003	2004	2005	2006	2007	2008	2009
Sales	(3)	(7)	134	286	545	579	541	490	683
Margin	7	9	102	171	320	371	373	382	490

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Reprioritization Summary		2001 Plan		"Roadmap" Reprioritization			
Total Spending (\$MM)		198		195		-2%	
Pre-Clinical thru Ph. III	Phase Mix						
	•Pre clin	13	(6%)	27	+100%	(14%)	NPS/ABS YM 579
	•Ph. I	47	(24%)	21	-55%	(11%)	Cox II TSP
	•Ph. II	10	(5%)	18	+80%	(9%)	ABL 594
	•Ph. III	128	(65%)	130	+2%	(66%)	ABL 627
	Therapeutic Area Mix						
	•AI	114	(58%)	88	-22%	(45%)	ABL 492
	•AV			0	-100%		KCO
	•U/C/D	5	(3%)				ABL 089
	•Neuro	15	(7%)	35	+133%	(18%)	NPS/ABS ABL 394 Cox II
	•Oncology	64	(32%)	72	+13%	(37%)	ABL 427 YM 529 TSP
Total Spending (\$MM)		102		105		+3%	
Phase IV	Therapeutic Area Mix						
	•AI	18	(18%)	5	-72%	(5%)	
	•AV	50	(57%)	62	+17%	(58%)	
	•U/C/D	1	(1%)	8	+600%	(3%)	
	•Neuro	24	(24%)	29	+21%	(27%)	

## Blue Plan Prioritization Proposal: Projects Prioritized by Expected Value

Foundation	Project Name	2001 Plan	Current Funding Request	Blue Plan: First \$25MM	Blue Plan: Next \$25MM	Blue Plan: Next \$25MM	Blue Plan: Next \$25MM	Total Blue Plan Funding	2001 Plan + Blue Plan
Neuroscience	Oral	24.1	30.3				3.2	11.5	29.5
	Cell	8.5	20.4	8.5			1.9	1.9	3.6
	AD 1-263	1.2	3.8						0.7
	AD 1-263	0.7	1.0					11.8	12.1
	AD 1-263	0.6	12.1	11.5					4.0
	AD 1-263	4.0	4.0				3.2	32.7	40.7
	AD 1-263	39.3	82.8	19.8	1.8	3.2	0.4	0.4	15.3
Anti-Infective	Oral	14.9	25.7					7.5	95.3
	Oral	4.8	15.3						24.8
	Oral	23.5	29.5						
	AD 1-263	23.5	39.8						
	AD 1-263	37.2					0.4	7.3	140.3
	AD 1-263	332.3	237.8						2.3
Urology/Cardiology	AD 1-263	2.3	11.8				6.0		7.4
	AD 1-263	1.4	13.4						6.0
	AD 1-263	5.0	4.5				6.9		14.7
	AD 1-263	8.7	29.7						4.0
HW Transplant	AD 1-263	4.0	8.7				1.0	11.1	12.1
	AD 1-263	61.0	89.8						2.5
	AD 1-263	2.5	2.5				1.5	11.1	70.2
	AD 1-263	37.3	60.3					18.2	57.8
	AD 1-263	38.8	68.0	3.2	11.5	4.0			7.4
Oncology	AD 1-263	7.4	3.0						2.9
	AD 1-263	10.0	12.5	2.0			1.5		12.9
	AD 1-263	6.4	10.0				0.8		8.8
	AD 1-263		4.1						
	AD 1-263								15.0
	AD 1-263		15.0		15.0			45.8	110.2
	AD 1-263	84.8	116.9	5.2	28.3	14.8			
Other	AD 1-263	118.3	118.3						18.3
	AD 1-263	118.3	118.3						
	AD 1-263	284.3	540.0	25.0	27.8	25.8	23.8	102.4	386.7
Total		284.3	540.0	25.0	27.8	25.8	23.8	102.4	386.7
APU Budget Assumption \$		284.3							

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**755**



Global Pharmaceutical R&D Strategy Retreat  
May 2-4, 2001

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**Abbott Oncology has a deep, diversified R & D portfolio that will vault us into a superior marketplace position, produce a highly profitable commercial franchise, and sustain long-term growth in a therapeutic area with the greatest unmet need**

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## **Abbott Oncology**

### **• Discovery**

- Focus on: 1) angiogenesis, 2) apoptosis, 3) signal transduction
- Leverage ABC for antibodies; exploit genomics, proteomics, expression profiling
- Consolidate oncology diagnostics R&D to pharmaceutical discovery: tumor load testing, antibodies

### **• Development**

- Efficiently demonstrate proof-of-principle: tumor response for cytotoxics and targeted therapy; blood tumor load/tumor tissue assays for cytostatics
- Abbott is paving the way for time to progression as an approvable endpoint: shorter timelines, earlier stages, chronic therapy
- Parallel studies of surrogate markers will facilitate use in proximal disease











### **• Commercial**

- Huge, growing unmet need: advanced disease and chronic therapy for earlier treatment
- Small SGA; premium pricing
- Accelerate commercial presence: in-license oxaliplatin, make an acquisition, Japanese earlier phase compounds

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EXECUTIVE SUMMARY - TA ASSESSMENT			 High  Low
Criteria	Assessment	Rationale	
1. Chronic diseases with expanding global markets		<ul style="list-style-type: none"> <li>Improved tolerability, side effect profile and delivery will enable chronic therapy for early and advanced disease</li> <li>Increased incidence and prevalence in aging population</li> </ul>	
2. Scientific opportunity		<ul style="list-style-type: none"> <li>Many 'validated' targets for 'cancer-selective' therapy</li> <li>Huge financial support for cancer research (NIH + philanthropy)</li> <li>Biologic (antibody) and small molecule approaches</li> <li>&gt;10% citations, 65,000 publications in 2000</li> </ul>	
3. Unmet medical need		<ul style="list-style-type: none"> <li>Epidemiology: 40% of people get cancer; 20% die from it</li> <li>Current therapy: marginal efficacy, toxic</li> <li>Treat early invasive disease: die with cancer (not from it); Improve quality of life for those with advanced disease</li> </ul>	
4. Opportunities for synergies with devices and diagnostics		<ul style="list-style-type: none"> <li>Tumor load testing/antibodies/diagnostic kits, monitor response</li> <li>Pharmacogenomics</li> <li>Therapy individualized by tumor genetics</li> <li>Targeted delivery devices; self injection devices for biologics</li> </ul>	
5. Competitive landscape		<ul style="list-style-type: none"> <li>Highly competitive: most pharma and many biotech have active programs</li> <li>~400 agents in (early) development (&gt;50% vaccines); few Ph III</li> <li>Seven players with &gt;\$500 MM sales</li> <li>Barrier to entry high, but barrier to subsequent competitors higher</li> </ul>	
6. Experience and expertise at Abbott		<ul style="list-style-type: none"> <li>4 years, 8 DDCs</li> <li>ABT-627 sets the standard for cytostatic drug development</li> <li>Innovative leaders in angiogenesis, apoptosis, antibodies (ABC), structural biology</li> <li>Ex-US Lupron sales; specialty audience commercialization</li> </ul>	
7. Fit with current marketed products or franchises		<ul style="list-style-type: none"> <li>Generics (including NaPro Paclitaxel)</li> <li>Diagnostics (PSA, HER2, etc), IV access, solutions/sets/pumps</li> <li>Good fit with pain, urology, CV (thrombosis), immunoscience franchises</li> <li>Nutritionals, nutraceuticals (Ross)</li> </ul>	
8. Balance of low, medium and high risk projects		<ul style="list-style-type: none"> <li>High risk: ABT-518, ABT-828, FTI, Tie2, Rubitecan, Pentumomab</li> <li>Medium risk: Bcl-X<sub>L</sub>, Akt, HDAC, ABT-510</li> <li>Low risk: ABT-751, ABT-627</li> <li>Need to in-license low risk, near term product(s)</li> </ul>	

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## EXECUTIVE SUMMARY – RECOMMENDATIONS

Disease focus	Drug pathways	Discovery molecular targets
<ul style="list-style-type: none"> <li>• More common cancers (breast, colorectal, prostate, lung, etc)               <ul style="list-style-type: none"> <li>– Advanced (metastatic, recurrent)</li> <li>– Locally invasive (stage I-III)</li> <li>– Early (e.g. PIN, DCIS, rectal carcinoma in situ) (future)</li> </ul> </li> <li>• Cancers with no approved therapy (hormone refractory metastatic prostate)</li> <li>• Cancers with marginally beneficial therapy (metastatic gastro-intestinal)</li> </ul>	<ul style="list-style-type: none"> <li>• Angiogenesis</li> <li>• Apoptosis</li> <li>• Signal transduction</li> <li>• Chromatin</li> <li>• Antibodies</li> </ul> <p><i>Development only:</i></p> <ul style="list-style-type: none"> <li>– Invasion/metastasis</li> <li>– Mitosis</li> </ul>	<ul style="list-style-type: none"> <li>• TSP mimetics, K5, Tie2, KDR, MetAP2</li> <li>• Bcl-X<sub>L</sub>, Akt, Survivin, XIAP</li> <li>• Endothelin axis, FTI, kinases</li> <li>• HDAC</li> <li>• Differentially-expressed cell surface epitopes</li> <li>• Matrix metalloproteinase</li> <li>• Tubulin</li> </ul>

**NOT DISCOVERY:** hormones, vaccines, gene therapy, supportive care, chemo/radio sensitizers, 'me too' cytotoxics.

**IN LICENSE:** hormones, chemotherapy, supportive care

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## CONTENTS

**Commercial  
outlook**

- Epidemiology across major regions
- Current TA sales by market segment and competitor
- Competitor portfolio review
- Global TA market drivers
- Major TA market trends to 2010
- Projected market growth by segment (e.g., disease, drug class)

Technical  
outlook

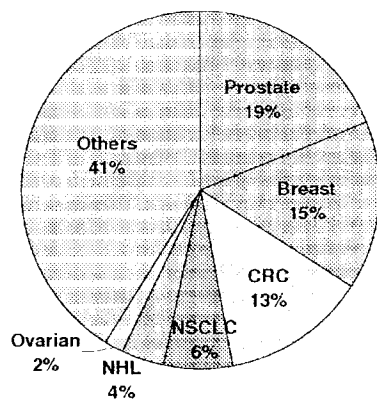
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## EPIDEMIOLOGY ACROSS TA

*Cancer Prevalence by Tumor Type (2000)  
Seven Major Markets*



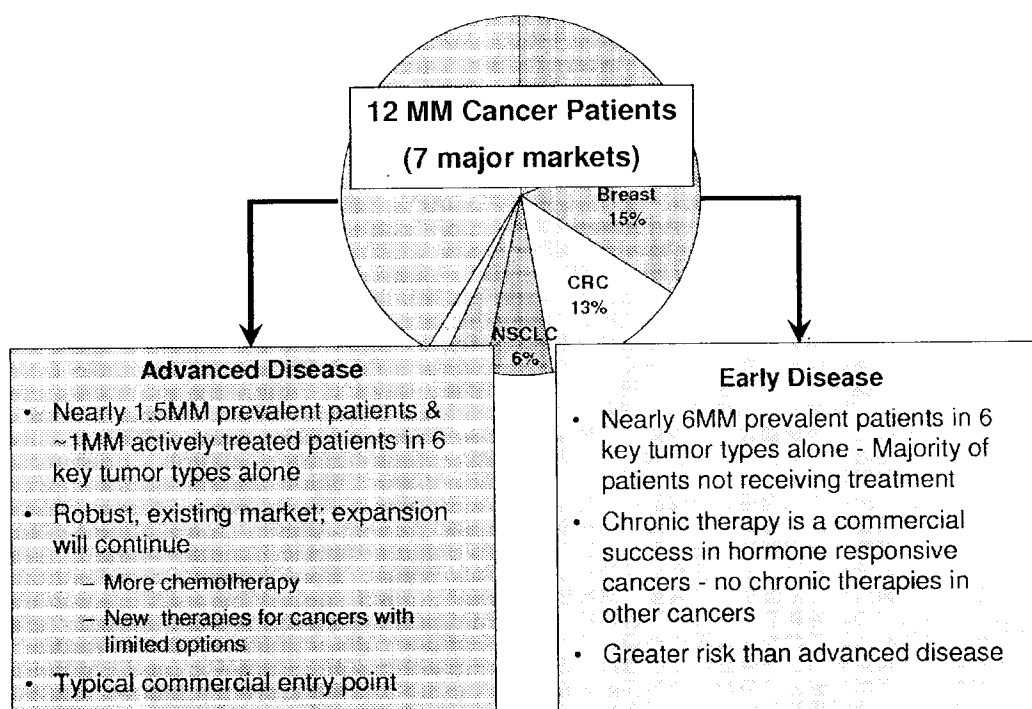
Total Prevalence: 12 MM

- Six key tumor types account for nearly 60% of global cancer patients
- Within remaining 40% opportunities remain
  - Tumors with no or limited therapeutic options (either on-label or off label)
  - Regionally prevalent cancers
    - Stomach cancer: ~265,000 patients in Japan vs. ~20,000 in US and ~65,000 in EU
    - Breast and prostate cancer: higher incidence in the western world than Asia

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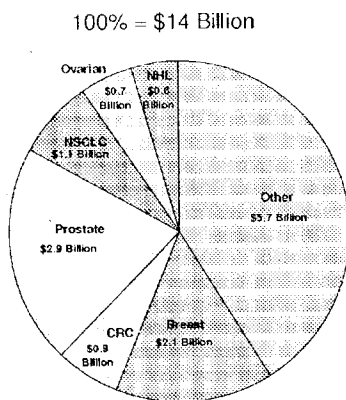
**EPIDEMIOLOGY ACROSS TA**


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**GLOBAL MARKET SEGMENTS AND FRANCHISE POSITION - 2000**

\$14 Billion: Chemotherapies and Hormones

*Worldwide Chemotherapeutic and  
Hormone Sales by Tumor Type*More than 50% of sales  
are in US**Franchise position: Emerging  
Abbott Sales: \$178MM (2000)**

Company	Total \$14,000 MM	Breast \$2,100 MM	NSCLC \$1,100 MM	Prostate \$2,900 MM	CRC \$900 MM	NHL \$600 MM	Ovarian \$700 MM
BMS	3,500	300	640	30		20	470
AstraZeneca	1,900	700		1,200			
Genentech/Roche	1,150	350			30	500	
Pharmacia	950	250			400	10	
Aventis	870	300	110	250	100		10
TAP	667			667			
Lilly	566	60	225				
Abbott	178			153			
Total	9,775	1,950	980	2,300	530	530	480

- Sales of supportive care products account for an additional \$4-5 billion worldwide
  - Supportive care products include hematopoietic growth factors, bisphosphonates and anti-emetics
  - Cancer pain management and nutritionals are not included

Sources: IMS, Wood MacKinzie, Davinci Healthcare Partners, Decision Resources

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## KEY COMPETITOR PORTFOLIO OVERVIEW

Disease	Late stage development (Pill)	Phase IV / commercialization
Breast Cancer	Leucotropin (Cangene); Detox (Corixa); EM-800 (Univ Laval); Atamestane (Schering); Arzoxifene (Lilly); Raloxifene (Lilly); Theratope (Biomira); Bevacizumab (Roche); Miproxifene Taiho; Losoxantrone (Pfizer); Fenretinide (McNeil)	Taxol (BMS), Arimidex (AZ), Nolvadex (AZ); Taxotere (Aventis); Herceptin (Roche); Elience (P&U); Femara (Novartis); Aromasin (P&U)
Prostate	Abarelix (Amgen-Sanofi); Cetrorelix (Asta); SPD-424 (Shire); AE-941 (Aeterna); CyPat (Barr); APC-8015 (Dendreon); Satraplatin (BMS)	Zoladex (AZ); Viadur (Alza); Casodex (AZ); Eulexin (Schering); Novantrone (Immunex)
Non-Hodkin's Lymphoma	Bexxar (Coulter-GSK); Epratuzumab (Immunomedics)	Rituxan (Roche)
NSCL	ZD-1839 (Iressa, AZ); Bevacizumab (Roche); AE-941 (Aeterna); Tirapazamine (Sanofi); Lanreotide (Beaufour-Ipsen); L651582 (Merck); ISIS-3521 (Isis); Gemtuzumab (P&U); BMS-275291 (BMS-CellTech)	Taxol (BMS), Taxotere (Aventis); Gemzar (Lilly); Parapiatin (BMS)
Ovarian	Sch-55560 (Schering); MDX-210 (Medarex); MAK-5AB (IDM); L651582 (Merck); Valspodar (Novartis)	Taxol (BMS), Parapiatin (BMS)
Colorectal	Oxaliplatin (Sanofi); Panorex (edrecolomab, Centocor-GSK); Bevacizumab (Roche); CTP-37 (ImmunoTherapy); Gastrimmune (Aventis-Aphton); OncoVAX-CL (intracel); rV-CEA (Titan-NCI); BMS-275291 (BMS-CellTech)	Camptosar (P&U)
Pancreatic	Irofulven (MGI); R-115777 (Janssen); Gastrimmune (Aventis-Aphton);	Gemzar (Lilly)

Abbott/Knoll  
BD activity\*:Active  
reviewConsidered-  
passedConsidered-  
lostNot  
availableNot  
considered

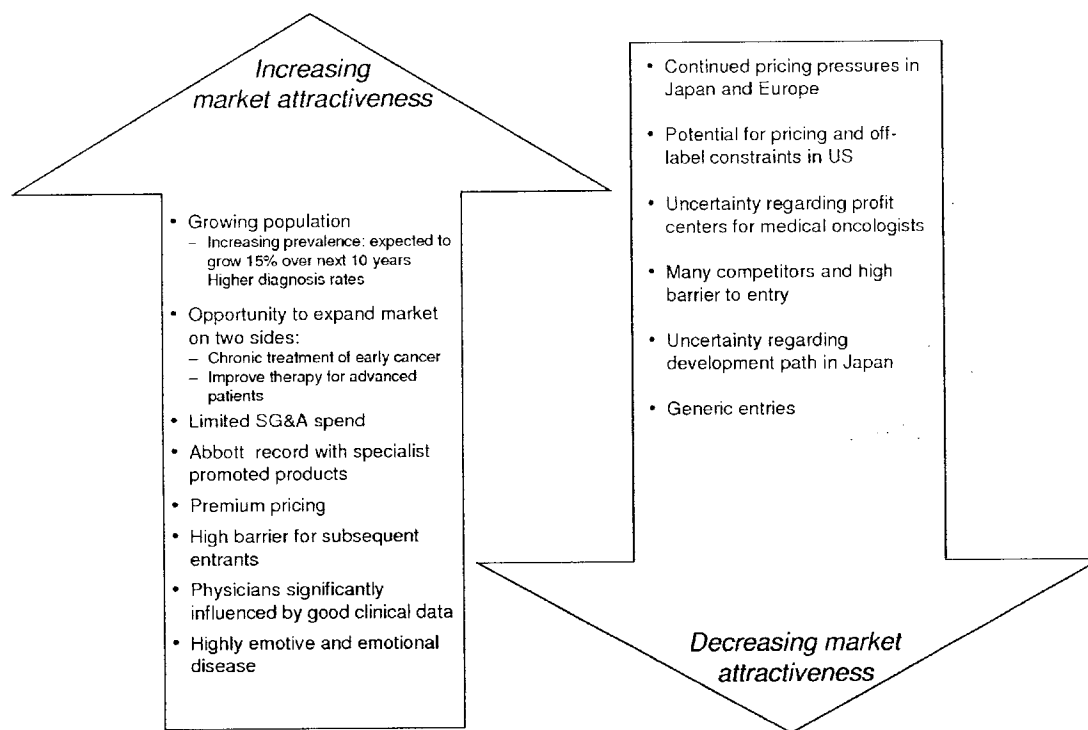
\* Color-code for target/NCE names in the table

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## GLOBAL TA MARKET DRIVERS



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**MAJOR TA MARKET TRENDS TO 2010**

	<u>Current situation</u>	→	<u>Projected situation in 2010</u>
<b>Global</b>	<ul style="list-style-type: none"> <li>• 12MM patients in 7 major markets</li> <li>• Most pharmaceutical therapies are acute (exception: hormones)</li> </ul>		<ul style="list-style-type: none"> <li>• More than 14MM patients in 2010</li> <li>• Physicians will use a combination of acute and chronic therapies in the majority of tumors</li> </ul>
<b>US</b>	<ul style="list-style-type: none"> <li>• Medicare offers limited reimbursement for oral cancer therapies</li> <li>• Cancer drugs account for 40-60% of medical oncologist's profit margin</li> </ul>		<ul style="list-style-type: none"> <li>• Medicare coverage for oral cancer therapies</li> <li>• Decreased reimbursement for office administered products</li> </ul>
<b>Europe</b>	<ul style="list-style-type: none"> <li>• Limited coverage for some expensive cancer medications</li> </ul>		<ul style="list-style-type: none"> <li>• Public outrage may force governments to cover cancer medications that offer clear mortality benefits</li> </ul>
<b>Japan</b>	<ul style="list-style-type: none"> <li>• Diagnosis often unknown to patient</li> <li>• Pricing flexibility</li> </ul>		<ul style="list-style-type: none"> <li>• More patients will be informed</li> <li>• Japanese government will more aggressively regulate pricing</li> </ul>
<b>ROW</b>	<ul style="list-style-type: none"> <li>• Older, less expensive cytotoxics first line</li> <li>• New therapy usage limited to privately insured</li> </ul>		<ul style="list-style-type: none"> <li>• Stabilization of economies and a &gt;% of privately insured will influence uptake of new treatments</li> <li>• Better access to diagnostics will increase number of treated patients</li> </ul>

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## PROJECTED GLOBAL TA MARKET GROWTH

\$ 14 Billion (2000)

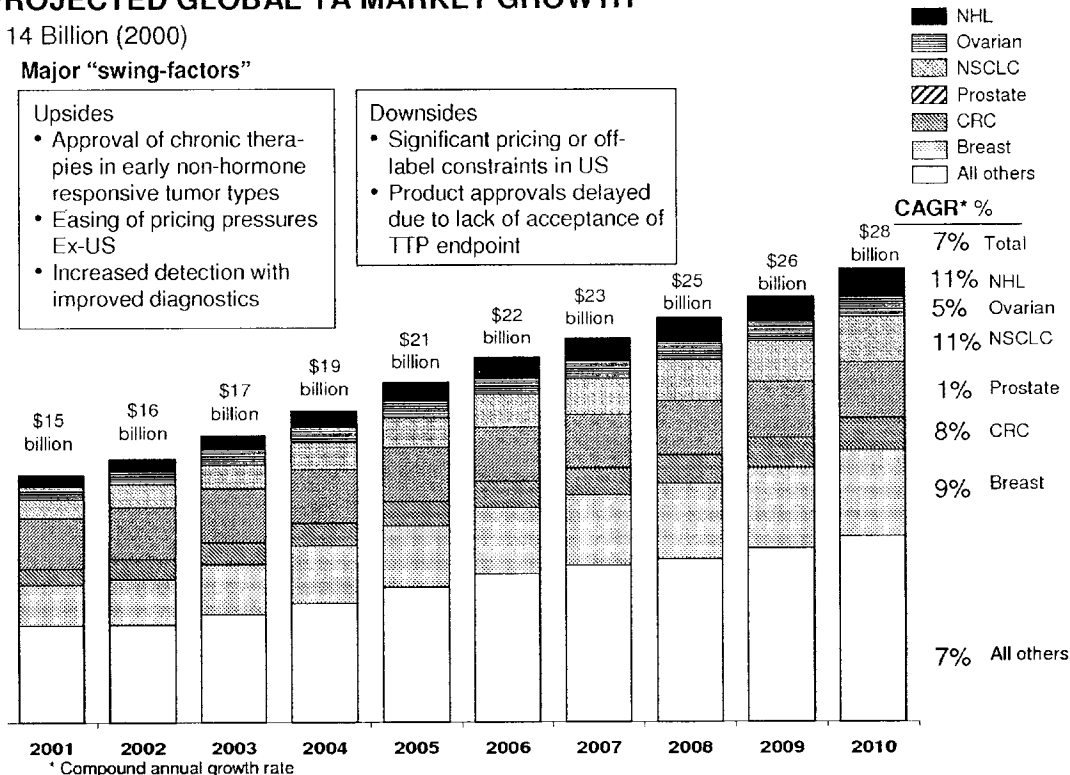
### Major "swing-factors"

#### Upsides

- Approval of chronic therapies in early non-hormone responsive tumor types
- Easing of pricing pressures Ex-US
- Increased detection with improved diagnostics

#### Downsides

- Significant pricing or off-label constraints in US
- Product approvals delayed due to lack of acceptance of TTP endpoint



Source: Decision Resources, Data Monitor, analyst reports, projections

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Commercial  
outlook

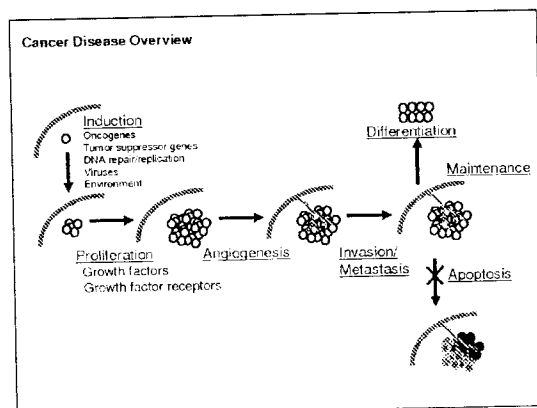
Technical  
outlook

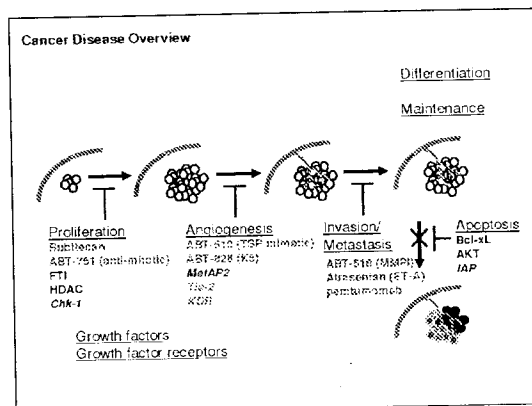
- Disease overview and new discovery opportunities
- Current treatment approach
- Current unmet needs
- Future medical practice
- Challenges and opportunities in discovery
- Challenges and opportunities in product development

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position

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## **CANCER DISEASE OVERVIEW**

### **• Causes**

- Genetic predisposition (sporadic & inherited mutations)
- Environment smoking (30%), occupational (5%), pollution (2%), UV (?)
- Infectious agents: hepatitis B & C, papilloma (HPV 16 and 18), EBV, herpesvirus, HTLV, Helicobacter pylori
- Diet
- Reproductive hormones

Why does cancer originate from only certain cell types/tissues?

### **• Epidemiology**

- 40% of people get cancer: 1/2 of men, 1/3 of women
- Prevalence 12 MM worldwide; Incidence 2.5MM worldwide
- 20% of people die from cancer: will be the most common cause of death in the USA and in Europe 2003; Already #1 in Japan
- Breast, colorectal, prostate and lung carcinoma: ~50% of all cancer (USA)
  - prostate (317,000 cases; 41,000 deaths), breast (186,000 cases; 45,000 deaths), lung (177,000 cases; 159,000 deaths), colorectal (134,000 cases; 55,000 deaths)
- Geographic variation: gastric and hepatocellular in Asia; melanoma in sunbelt
- Incidence and prevalence increasing (age); 30% due to smoking

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## **CANCER DISEASE OVERVIEW**

- **Clinical Features**

- Generally, patients don't die from the primary tumor
- Metastases/Invasion
- Sequelae of therapy
- Cure vs disease stabilization/chronic therapy: antibiotic paradigm won't work
- Quality of life

- **Current treatment:** curative intent: ineffective and toxic.

- Surgery, radiation, chemotherapy. Rationale: target dividing tumor cells
- Hormones, biologics (cytokines, antibodies)
- Some success: lymphoma, germ cell, childhood cancer; early breast Ca.
- No significant improvement for the more common cancers and overall age-adjusted mortality is increasing
- Refinements in use of current agents (amount, combination): modest incremental benefit
- Annual economic cost: \$104 BB (USA)

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<b>Non-Small Cell Lung Cancer</b> <u>Primary treatment:</u> -Surgery if operable (curative) -Radiotherapy if locally advanced <u>Adjuvant therapy:</u> -Clinical trial <u>Locally advanced/recurrent/metastatic:</u> -Chemotherapy (paclitaxel, vinorelbine, gemcitabine/platinum) -Clinical trial	<b>Prostate Cancer</b> <u>Primary treatment:</u> -Surgery-radical prostatectomy/nerve-sparing procedures -Radiation therapy <u>Adjuvant therapy:</u> -Androgen ablation (surgical/hormonal)? <u>Locally advanced/recurrent/metastatic disease:</u> -Radiation therapy for palliation (local, bone) -Androgen ablation (bicalutamide, LHRH antagonists) -Cytotoxic chemotherapy (docetaxel, estramustine, mitoxantrone) -Clinical trial - ABT-827
<b>Lung Cancer (Small Cell):</b> <u>"Limited" and "extensive" categories:</u> -Probably all are systemic -Surgery (rare, isolated) -Cytotoxic chemotherapy (paclitaxel, cisplatin, etoposide) -Clinical trial <u>Adjuvant therapy:</u> -Prophylactic cranial irradiation if remission obtained <u>Therapy for recurrence:</u> -Chemotherapy (topotecan, CAV) -Clinical trial	<b>Pancreatic cancer</b> <u>Primary treatment:</u> -Surgery (curative if detected early - rare, incidental) <u>Adjuvant therapy:</u> -Chemoradiation (5-FU as radiosensitizer) <u>Locally advanced/recurrent/metastatic:</u> -Gemcitabine (survival extension <2 mos) -5-FU variations -Rubicin? -Clinical trial
<b>Colorectal carcinoma</b> <u>Primary treatment:</u> -Surgery <u>Adjuvant therapy:</u> -Radiation (rectal) -5-FU/leucovorin/irinotecan -Clinical trial (5-FU variations, oxaliplatin) <u>Recurrent/metastatic disease:</u> -Surgery - isolated liver mets -Repeat 5-FU/irinotecan -Oxaliplatin (clinical trials)	<b>Non-Hodgkin's Lymphoma:</b> <u>Aggressive histiologies:</u> <u>Primary Treatment (Sézary disease):</u> -Aggressive chemotherapy - CHOP is standard of care -Aggressive non-ablative therapy no better (ProMace, MACOP-B) -Role of marrow ablation? Autologous stem cell transplant <u>Relapse/Salvage:</u> -MAb: Rituximab (moving to frontline) -Marrow ablation/hemopoietic growth factor -Salvage cytotoxic chemotherapy -CNS: intrathecal cytarabine (Depocyt) <u>Indolent histiologies, localized (rare):</u> -Rituximab, interferon, fludarabine, 2 chloroadenosine, 2 deoxycorynycin (inhibit ADA)
<b>Breast Cancer</b> <u>Primary treatment:</u> -Surgery (typically lumpectomy) nodes -Neoadjuvant chemotherapy -Radiation <u>Adjuvant therapy:</u> -Cytotoxic chemotherapy (CMF, doxorubicin, paclitaxel) -Hormone therapy (tamoxifen) <u>Recurrent/metastatic disease:</u> -Salvage chemotherapy (docetaxel, capecitabine, liposomal doxorubicin) -Hormonal therapy (SERMs, aromatase inhibitors) -Herceptin +/- paclitaxel -Bisphosphonates (osteolytic bone mets)	<b>Leukemias:</b> <u>Acute:</u> -Marrow ablation +/- marrow/stem cell support -Anthracyclines, vinca alkaloids, many other cytotoxics -High dose steroids (ALL) -Myelotarg (MAb with "payload" cytotoxic activity for salvage) <u>Chronic:</u> -Alpha-interferon, hydroxyurea -Marrow ablation/transplant can be curative (CML) -Glivec: targeted to BCR/ABL gene product (dramatic Phase I/II data)



<b>Stomach</b> <u>Primary treatment:</u> -Surgery (extensive node dissection in Japan) -? better results? <u>Adjuvant therapy:</u> -Chemoradiation? (preliminary ASCO report) -Clinical trial <u>Recurrent/metastatic disease:</u> -Palliation: radiation, chemotherapy -Clinical trial	<b>Malignant Melanoma</b> <u>Primary treatment:</u> -Surgery (local excision/lymph node mapping/dissection) <u>Adjuvant therapy:</u> -Interferon (high risk for recurrence) <u>Recurrent/metastatic disease:</u> -Palliative surgery, radiation, chemotherapy -Interleukin-2 -Clinical trial
<b>Ovarian Cancer</b> <u>Primary treatment:</u> -Surgery (debulking) -Chemotherapy (paclitaxel, carboplatin, cyclophosphamide) <u>Adjuvant therapy:</u> -None, consider clinical trial (peritumomab) <u>Recurrent/metastatic disease:</u> -Salvage chemotherapy (taxane, topotecan, liposomal anthracycline) -Clinical trial	<b>Brain (Adult Glioblastoma)</b> <u>Primary treatment:</u> -Surgery (steroids, anticonvulsants) -Often incomplete due to anatomy/tumor biology -Radiation therapy if inoperable <u>Adjuvant therapy:</u> -Radiation therapy -Incomplete resection/local recurrence: -"Gliadel wafer" - cytotoxic "device" (BCNU) -Palliation: radiation, steroids -Clinical trial
<b>Bladder Cancer</b> <u>Primary treatment:</u> -Non-invasive disease: Intravesical BCG, mitomycin, anthracycline -Invasive disease: radical surgery (cystectomy) <u>Adjuvant therapy:</u> -Cytotoxic chemotherapy (M-VAC): benefit? <u>Recurrent/metastatic disease:</u> -Palliative cytotoxic chemotherapy -Clinical trial	<b>Endometrial Cancer:</b> <u>Primary treatment:</u> -Surgery <u>Adjuvant therapy:</u> -Radiation <u>Recurrent/metastatic disease:</u> -Endocrine therapies (SERMs, Megace) -Palliative cytotoxic chemotherapy (carboplatin, taxane, anthracycline) -Clinical trial
<b>Renal Cell</b> <u>Primary treatment:</u> -Surgery - resection -Arterial embolization <u>Adjuvant therapy:</u> -Clinical trial <u>Recurrent/metastatic disease:</u> -Interleukin-2 -Chemotherapy (vinblastine) -Clinical trial	

## SUMMARY OF MAJOR UNMET NEEDS

Category	Major unmet needs				
	General	Prostate	Breast	Colorectal	Lung
1. Prevention	•Formidable studies, time, money •Safety	•Finasteride?	•SERMs	•Cox-2	•No smoking
2. Diagnosis	•Pre-symptomatic, pre-metastatic detection paramount •Pharmacogenomics •Tumor genotype	•PSA (partly met)	•Mammography (unmet)	•Endoscopy (unmet)	•Spiral CT/CXR, sputum cytology (unmet)
3. Treatment					
- Efficacy	•Marginal	•Androgen ablation •Radiation, surgery •No Rx for advanced disease	•Radiation, surgery •Adjuvant CMF • Anthracyclines, Taxanes, Herceptin	•5FU, Capecitabine ~15% survival	•Radiation, surgery •Carboplatin + X
- Safety	•Myelosuppression •Nausea, vomiting, diarrhea •Mucositis •Renal, cor, neuro •Alopecia	•Loss of libido •Gynecomastia •Hot flashes •Osteopenia	•Cardiomyopathy •Neurotoxicity •Capillary leak	•Diarrhea	•Nephrotoxicity, ototoxicity
- Compliance	•?↓ for oral drugs				

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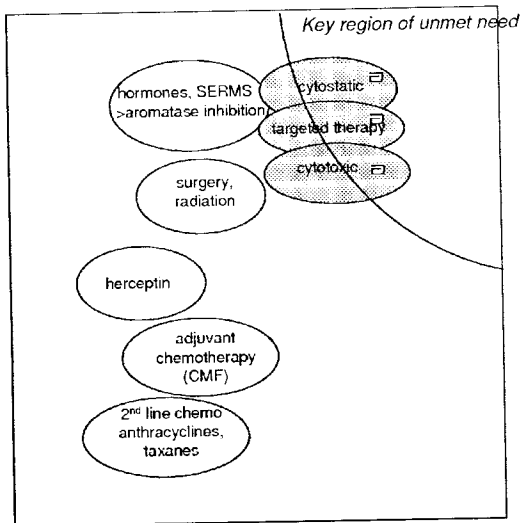
## MAJOR UNMET NEEDS – BY DISEASE

Breast Cancer

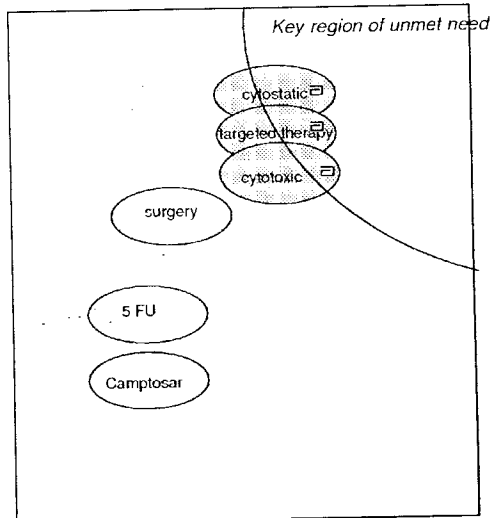
Colorectal

Tolerability

Tolerability



Efficacy



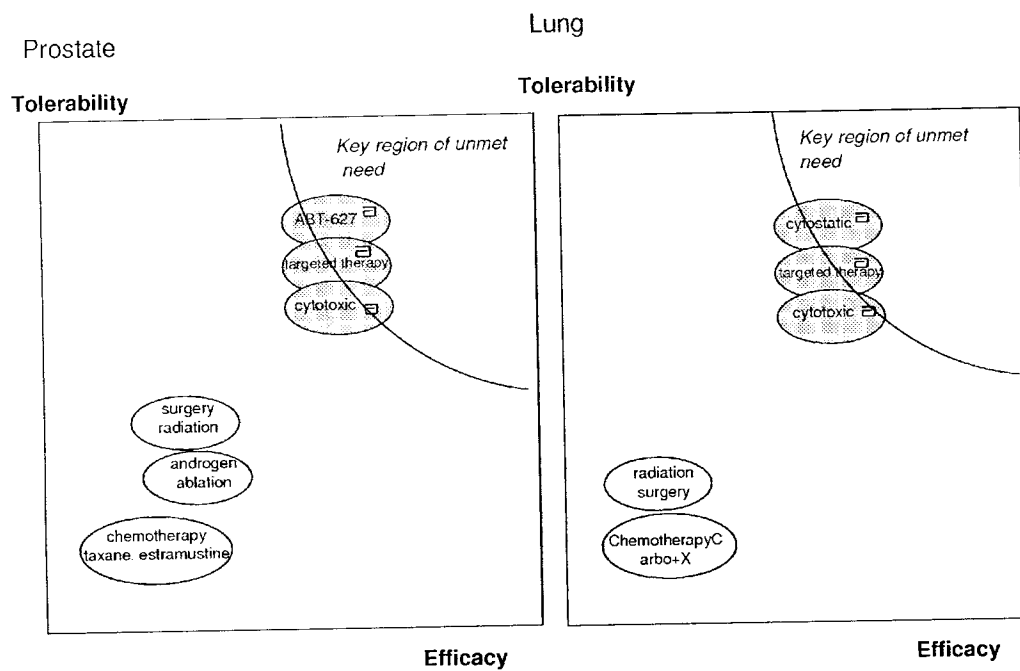
Efficacy

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## MAJOR UNMET NEEDS – BY DISEASE



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## FUTURE MEDICAL PRACTICE IN 2010- ONCOLOGY

### Current practice

- Acute therapy, shrink tumors/curative intent
- Parenteral, bolus, cytotoxic chemotherapy
- Hormone therapy (parenteral and oral)
- Open surgical resection of primary tumor
- External beam radiation for local control
- No 'cytostatic' therapy  
(but hormone therapy is similar paradigm)
- Limited tumor-targeted therapy (antibodies)
- Limited chemoprevention
- Therapeutic response measured by radiographic imaging (MRI, CT, etc.), limited use of surrogate markers
- Common treatment according to histology and grade/stage. Titrate to toxicity. No genotyping
- Parenteral growth factors
- Treat acute emesis (5HT-3)
- Three therapeutic antibodies






### Future practice (2010)








- Chronic therapy/disease stabilization
- Chronic, oral "metronomic" chemotherapy
- Oral/patch/depot hormone therapy
- Laparoscopic surgery, fewer resections
- Brachytherapy, stereotactic
- Chronic, oral cytostatic therapy: angiogenesis inhibitors
- Acute and chronic tumor-selective therapy: apoptosis and signal transduction
- SERMs, Cox-2, angiogenesis inhibitors,
- Blood pharmacodynamic measures (tumor load testing), more robust surrogate markers, sentinel node
- Pharmacogenomics,
- Therapy individualized by tumor genotype
- Small molecule, oral growth factor mimetics
- Treat delayed emesis (NK1?)
- Multiple therapeutic antibodies & diagnostics

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## DISCOVERY OPPORTUNITIES AND CHALLENGES

 Advantages  
   
 Disadvantage

Issue	Assessment	Rationale
1. Are viable/tractable targets currently available?		<ul style="list-style-type: none"> <li>Literature</li> <li>Academic collaborators</li> <li>Small companies</li> <li>Many tractable targets (e.g. kinases and proteases)</li> </ul>
2. Are attractive sources of new targets available?		<ul style="list-style-type: none"> <li>Academic collaborations (Abbott/dun, SAE, Wang)</li> <li>Proprietary tools (survivin, K5) for target discovery</li> <li>Public domain targets and ad hoc license opportunities</li> <li>Incyte collaboration for proprietary antibody targets</li> <li>Genomics, proteomics, expression profile collaboration(s)</li> </ul>
3. How powerful are current target validation strategies?		<ul style="list-style-type: none"> <li>Excellent cell-based target validation</li> <li>Many genetic knock-outs and antisense studies</li> <li>Challenging to distinguish target specificity versus toxicity</li> </ul>
4. Do viable <i>in vitro</i> models of the diseases exist?		<ul style="list-style-type: none"> <li>Many cancer cell lines available</li> <li>Proliferation, transformation, migration, invasion angiogenesis, apoptosis readily evaluated</li> </ul>
5. Do viable <i>in vivo</i> models exist (e.g., transgenics)?		<ul style="list-style-type: none"> <li>Human tumor xenografts (growth, angiogenesis and metastasis)</li> <li>Multiple techniques to evaluate disease progression</li> <li>Surrogate models for angiogenesis and invasion</li> <li>Transgenic models for study of disease initiation, none for maintenance</li> <li>Companion animals</li> </ul>
6. How predictive are pre-clinical models?		<ul style="list-style-type: none"> <li>Limited prediction of efficacy/spectrum of activity from conventional rodent models</li> <li>Reliable determination of specificity/side effects</li> <li>Newer mouse models may be more predictive</li> <li>Sporadic cancers in dogs may mirror human disease</li> </ul>
7. Strength of applicable discovery expertise at Abbott		<ul style="list-style-type: none"> <li>Outstanding med. chem., structural biology, HTS</li> <li>Strengths in kinases, antibody technology, angiogenesis, apoptosis</li> <li>Support needed: <i>in vitro</i> and <i>in vivo</i> biology</li> </ul>

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**VIABLE MOLECULAR TARGETS**
☐ Significant Abbott presence

Potential targets	Lead competitors	Scientific rationale
1. Angiogenesis (K5, TSP peptides, Met AP2, Tie-2, KDR) <i>angiostatin, endostatin</i>	• P & U/Sugen, Novartis, Entremed, TAP, Pfizer, BMS	<ul style="list-style-type: none"> <li>• Essential endothelial cell growth factors</li> <li>• Endogenous inhibitors</li> <li>• block neo-vessels</li> </ul>
2. Apoptosis (Bcl-2, Akt, IAP), <i>caspases</i>	• Genta, Structural Bioinformatics, Novartis, Lilly, Amgen/Kinetix, Kinetek, Pharmacia, Janssen, Pfizer, Schering, Tularik	<ul style="list-style-type: none"> <li>• major form of resistance</li> <li>• hallmark of cancer</li> </ul>
3. Signal Transduction (Flase, cMet, IGF-1r, Rce1) <i>EGFR, other RTKs</i>	• Janssen, BMS, Schering, Merck, Pfizer, Astra Zeneca, Novartis, Amgen, Genentech	<ul style="list-style-type: none"> <li>• autocrine growth factors, constitutive activation of receptors, signal cross talk</li> </ul>
4. Cell Cycle (antimitotic, Chk-1, Wee-1, Plk1) <i>CDKs</i>	• BMS, Merck, Tularik, Chiron, Bayer, GSK, Pfizer, Roche, Novartis	<ul style="list-style-type: none"> <li>• inhibit mitosis</li> <li>• abrogate G2 checkpoint</li> <li>• Inhibit cell cycle progression</li> </ul>
5. Chromatin Regulation (HDAC) <i>DNA methyl transferase, HAT</i>	• Sloan Kettering, Fujisawa, Mitsui, Pfizer, Novartis, SuperGen, Chroma Therapeutics	<ul style="list-style-type: none"> <li>• Epigenetic/transcriptional regulation of malignant phenotype</li> </ul>
6. Antibodies (Pemtumomab) <i>Growth factor receptors</i>	• Genentech, Medarex, Abgenix, Imclone	<ul style="list-style-type: none"> <li>• growth factor receptors</li> <li>• proteins selectively expressed on the surface of tumor cells</li> </ul>

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**POTENTIAL SOURCES OF NEW TARGETS**
☐ Significant Abbott presence

Source	Scientific rationale
1. Tumor Biology	<ul style="list-style-type: none"> <li>• signal transduction, cell cycle, DNA repair</li> <li>• initiation, progression, maintenance, resistance</li> <li>• apoptosis, angiogenesis, metastasis</li> </ul>
2. Expression Profiling	<ul style="list-style-type: none"> <li>• overexpressed in tumor vs. normal cells</li> <li>• overexpressed in activated ECs</li> </ul>
3. Proteomics	<ul style="list-style-type: none"> <li>• overexpressed in tumor vs. normal cells</li> <li>• overexpressed in activated ECs</li> </ul>
4. Random Gene Knockouts	<ul style="list-style-type: none"> <li>• Ribozymes (Imusol, RPI)</li> <li>• Zinc fingers (Sangamo)</li> <li>• Molecular Biology (Athersys)</li> <li>• Virus (Quark)</li> </ul>
5. Association Genetics	<ul style="list-style-type: none"> <li>• DeCode, Gemini, Oxygen, Myriad</li> </ul>
6. Database Mining/Bioinformatics	<ul style="list-style-type: none"> <li>• Homologous proteins</li> <li>• Motif discovery</li> </ul>




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## PRODUCT DEVELOPMENT OPPORTUNITIES AND CHALLENGES

 Advantage  
   
 Disadvantage




Issue	Assessment	Rationale
1. Are viable proof-of-concept methodologies available?		<ul style="list-style-type: none"> <li>• Tumor response, survival (cytotoxics)</li> <li>• Time to progression (cytostatics)</li> <li>• Pharmacodynamics (needed)</li> </ul>
2. Is patient recruitment a major obstacle?		<ul style="list-style-type: none"> <li>• Depends on disease category and available options; increasing competition for patients, yet &lt;5% participate in trials, clinical trial is standard of care = reimbursement</li> </ul>
3. Are clinical trial guidelines available?		<ul style="list-style-type: none"> <li>• FDA/EMA guidance is available for some clinical endpoints and/or disease categories, ICH guidelines</li> <li>• ABT-627 blazing the pathway for cytostatics</li> </ul>
4. Is trial methodology easy/difficult?		<ul style="list-style-type: none"> <li>• Methodology is easy to develop, but can be moderately difficult to execute (e.g., placebo controls, compliance with frequent assessments)</li> </ul>
5. Are validated outcome measures available?		<ul style="list-style-type: none"> <li>• Yes, for tumor response, survival (unequivocal)</li> <li>• Measurement of clinical progression and quality of life is evolving</li> </ul>
6. Is placebo or comparator response rate high?		<ul style="list-style-type: none"> <li>• No, for tumor response or survival. Quality of life assessment less robust</li> <li>• Current therapies are mostly ineffective and toxic</li> </ul>
7. Is there major adverse experience liability?		<ul style="list-style-type: none"> <li>• No. Practitioners, patients and regulatory authorities tolerate significant toxicity if there is efficacy.</li> </ul>







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## PRODUCT DEVELOPMENT OPPORTUNITIES AND CHALLENGES (Continued)

 Advantage  
   
 Disadvantage

Issue	Assessment	Rationale
8. Level of investment required (trial size, length, complexity)		<ul style="list-style-type: none"> <li>Survival for frontline therapy of earlier disease takes longer</li> <li>Clinical progression endpoint has shorter duration but more complexity and regulatory risk</li> </ul>
9. Level of Abbott clinical development expertise across the TA		<ul style="list-style-type: none"> <li>5 oncologists</li> <li>No Abbott NDA/BLA, but Ph I-IV outside experience</li> <li>Great advisors/consultants</li> </ul>
10. Is the regulatory path well established (across major markets)?		<ul style="list-style-type: none"> <li>Limited coordination/communications between FDA, CPMP, KIKO, despite ICH guidelines</li> </ul>
11. Is the indication recognized by regulators in US, Europe, Japan?		<ul style="list-style-type: none"> <li>Yes for treatment of advanced disease and hormone therapy</li> <li>No for "locally invasive", premalignant disease or chemoprevention</li> </ul>
12. Overall regulatory risk of development?		<ul style="list-style-type: none"> <li>Positive, interactive relationship with FDA (ABT-627); working on EMEA and Koseisho</li> </ul>
13. Level of Abbott regulatory expertise across the TA		<ul style="list-style-type: none"> <li>Two with (outside Abbott) oncology experience currently in HPD</li> </ul>

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## ATTRACTIVE DRUG PATHWAYS IN CLINICAL DEVELOPMENT

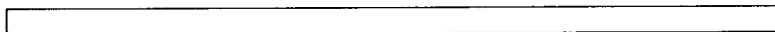
☐ Significant Abbott presence

Drug pathway	Lead compounds	Scientific rationale
1. Endothelin Axis	<ul style="list-style-type: none"> <li>•ABT-627 (Abbott)</li> <li>•YM598 (Yamanouchi)</li> </ul>	<ul style="list-style-type: none"> <li>•Antiproliferative, inhibits osteoblasts/skeletal metastases, anti-nociceptive</li> </ul>
2. Angiogenesis	<ul style="list-style-type: none"> <li>•ABT-510 (Abbott)</li> <li>•ABT-828 (Abbott)</li> <li>•BSF404578 (Abbott)</li> <li>•BSF476921 (Abbott)</li> <li>•RhuMAbVEGF (Genentech)</li> <li>•SU5416,6668 (P&amp;Y, Sugen)</li> <li>•PTK787 (Novartis), ZD6474 (Astra Zeneca), GW2286 (GSB)</li> </ul>	<ul style="list-style-type: none"> <li>•Thrombospondin mimetic, broad inhibitor</li> <li>•K5 plasminogen fragment, broad inhibitor</li> <li>•Tie2, key step in neovascularization</li> <li>•KDR/VEGF, best characterized pro-angiogenic growth factor (variable selectivity- some hit PDGF, etc)</li> </ul>
3. Apoptosis	<ul style="list-style-type: none"> <li>•A-371191 (Abbott)</li> <li>•G3139 (Genta)</li> <li>•A-396829 (Abbott)</li> </ul>	<ul style="list-style-type: none"> <li>•Bcl-X<sub>L</sub> nodal regulator</li> <li>•Bcl, antisense</li> <li>•Akt, PTEN evidence</li> </ul>
4. Mitosis	<ul style="list-style-type: none"> <li>•ABT-751 (Abbott)</li> <li>•T138067 (Tularik)</li> <li>•Combretastatin A4 (BMS)</li> <li>•Epo 906 (BMS)</li> <li>•BMS 188797, 184476</li> </ul>	<ul style="list-style-type: none"> <li>•Oral, non-MDR substrate, colchicine site binder</li> <li>•Colchicine site binder</li> <li>•Colchicine site binder, vascular targeting</li> <li>•Epothilone family</li> <li>•Novel taxanes</li> </ul>
5. Farnesyltransferase	<ul style="list-style-type: none"> <li>•Sch66336 (Schering)</li> <li>•R115777 (Janssen)</li> <li>•BMS 193269 (BMS)</li> <li>•CP60974 (Pfizer)</li> <li>•A-409100 (Abbott)</li> </ul>	<ul style="list-style-type: none"> <li>•Target known, substrate uncertain, proof of principle for several cancers</li> </ul>
6. Matrix metalloproteinase	<ul style="list-style-type: none"> <li>•Prinomastat (Agouron/Pfizer), BMS276291 (BMS), ABT-518 (Abbott)</li> </ul>	<ul style="list-style-type: none"> <li>•Inhibit invasion, metastasis, angiogenesis</li> <li>•gelatinase A/B selective</li> </ul>
7. Chromatin	<ul style="list-style-type: none"> <li>•MS275 (Mitsui), SAHA (MSKCC)</li> <li>•FK228 (Fujisawa)</li> </ul>	<ul style="list-style-type: none"> <li>•HDAC inhibitors</li> </ul>
8. Antibodies	<ul style="list-style-type: none"> <li>•Pentumomab (Abbott/Antisoma)</li> <li>•C225 (ImClone), others</li> </ul>	<ul style="list-style-type: none"> <li>•Tumor- targeted therapy</li> </ul>

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## ATTRACTIVE DRUG PATHWAYS IN CLINICAL DEVELOPMENT

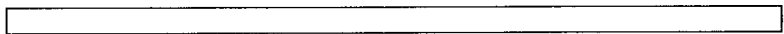
☐ Significant Abbott presence

Drug pathway	Lead compounds	Scientific rationale
8. Signal transduction RTK/EGFR	•Iressa (AstraZeneca) •C225 (ImClone)	•EGFR small molecule antagonist, key proliferative signal for epithelial cancers •EGFR antibody
9. bcr-abl	•Glivec (Novartis)	•Translocation/fusion RTK, in CML
10. SERMs	•Evista (Lilly)	•Beats tamoxifen
11. Bisphosphonates	Zometa (Novartis)	•Prevent/treat skeletal metastases
12. Neurokinin 1	• MK869(Merck)	•Delayed emesis from chemotherapy
13. Platinum cytotoxics	•Oxaliplatin (Sanofi) •Satraplatin (BMS)	•Less nephrotoxic or myelosuppressive, active in colorectal carcinoma
14. LHRH pure antagonists	•Abarelix (Amgen) •Cetrorelix (AstaMedica)	•No surge
15. Antimetabolite cytotoxics	AD9331 (AstraZeneca), LY231415 (Lilly),	•Beats 5-FU, methotrexate, oral

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## CONTENTS

Commercial  
outlook

Technical  
outlook

**Abbott  
position**

- Current Abbott sales
- Abbott's current TA portfolio, budget allocation and risk profile
- Upside scenario (sales potential; what we need to achieve the upside)

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**GLOBAL ABBOTT SALES - 2000**

\$178 Million

- Franchise position: Emerging
- Abbott pharmaceutical sales in oncology totaled \$178MM
  - Sales of Lupron in smaller European markets (\$153 MM)
  - HPD generics (\$25 MM)

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**OVERVIEW OF CURRENT R&D PROGRAMS**

2001 planned budget; \$millions

R&D program	Discovery			Development			On-market	
	Explor.	Lead opt.	Cand. select.	I	II	III	IIIb	IV
<b>Angiogenesis</b>								
TSP			3.0	10.8				
K5			4.6					
TSP backup	1.0							
Met AP2			4.7					
Tie-2		5.5						
KDR								
<b>Apoptosis</b>								
Bcl-2			5.8					
Akt	0.2	5.5						
IAP								
<b>Metastasis</b>								
MMPI				7.0				
<b>Proliferation/</b>								
<b>Cell cycle</b>								
ET antagonist				1.9	1.0	35.5		
Antimitotic				8.3				
FTI			6.8					
HDAC		5.0						
Chk-1	1.0							
New kinase target	1.0							
<b>Totals</b>	<b>3.2</b>	<b>16</b>	<b>24.9</b>	<b>28.0</b>	<b>1.0</b>	<b>35.5</b>		

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**RISK PROFILE OF THE CURRENT PORTFOLIO**

33% Current Trajectory; 29% Overall

H - High risk (0-20%)  
M - Medium risk (21-40%)  
L - Low risk (41-100%)

R&D program	Discovery probability of success (%)	Development probability of success (%)	Regulatory probability of success (%)	Commercial probability of success (%)	Overall risk assessment (%)
<b>Angiogenesis</b>					
K5	90	26	80	80	H (17)
TSP	-	26	80	80	M (23)
Tie-2	75				
KDR	50				
K5 back-up	25				
TSP back-up	75	36	80	80	H (17)
Met AP2	25				
<b>Apoptosis</b>					
Bcl-2	50				
Akt	50				
IAP	25				
<b>Metastasis</b>					
MMPI	-	18	80	80	H (12)

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**RISK PROFILE OF THE CURRENT PORTFOLIO**

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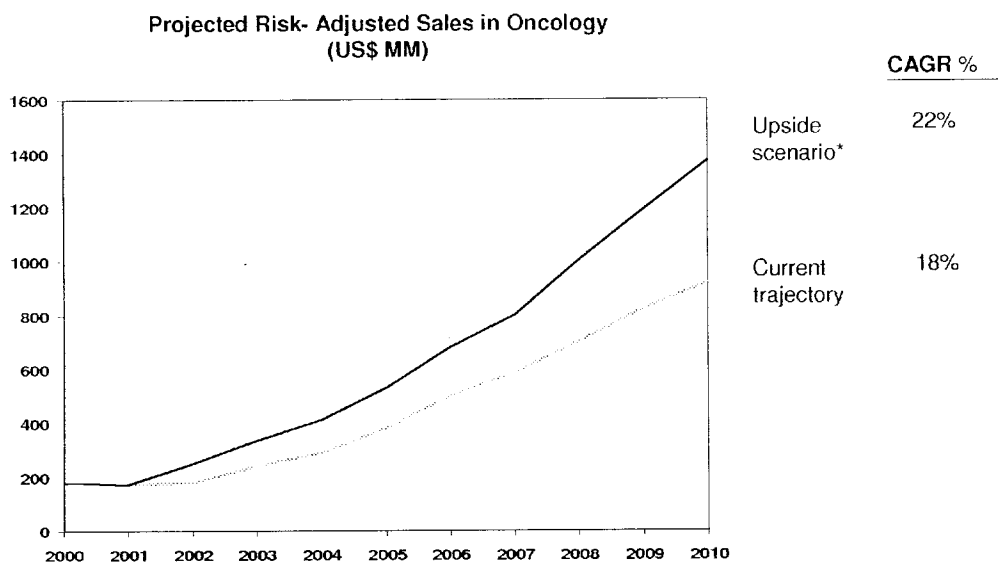
R&D program	Discovery probability of success (%)	Development probability of success (%)	Regulatory probability of success (%)	Commercial probability of success (%)	Overall risk assessment (%)
<b>Proliferation</b>					
Atrasentan Base	-	80	90	90	L (65)
Atrasentan-Early PCa					
Atrasentan-Chemo Combo					
Atrasentan-Bisphosphonate Combo					
Atrasentan-Other Cancers					
Antimitotic	-	34	90	80	M (24)
FTI	75	17	80	80	H (8)
HDAC	50				
Chk-1	25				
Rubitecan		50	50	75	H (19)
Pentumamab		28	90	90	M (23)
<b>Marketed Products</b>					
Lupron (AI)				90	H (90)
HPD				75	H (75)

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## GROWTH SCENARIOS FOR THE TA

Risk adjusted sales; \$ 919 MM Current Trajectory  
\$1,400 MM Upside



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## GROWTH OPPORTUNITIES TO ACHIEVE UPSIDE SCENARIO

	Description of upside opportunity*	Requirements to capture opportunity
<b>Discovery</b>	<ul style="list-style-type: none"> <li>• Improve in vivo tumor biology</li> <li>• Antibodies (diagnostic and therapeutic)</li> <li>• Proteomics/expression profiling</li> </ul>	<ul style="list-style-type: none"> <li>• Dana Farber collaboration or other</li> <li>• Leverage ABC capability</li> <li>• Collaborate with Rosetta, Eos, others</li> </ul>
<b>Development</b>	<ul style="list-style-type: none"> <li>• Expand ABT-627 use in prostate cancer (pre-Lupron treat PSA, salvage + chemo)</li> <li>• Other cancer indications for ABT-627</li> <li>• ABT-828; non-oncology indications for angiogenesis inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>• Internal funding, or</li> <li>• partner (NCI; commercial), or</li> <li>• alternative financing</li> </ul>
<b>In-licensing</b>	<ul style="list-style-type: none"> <li>• License-in (co-develop/co-promote) late stage or marketed lower risk compound</li> <li>• License-in earlier stage lower risk compounds</li> </ul>	<ul style="list-style-type: none"> <li>• Freedom to pursue creative deal structures (share, JV, partnerships, etc)</li> <li>• Oxaliplatin (Sanofi-Synthelabo)</li> <li>• Japanese companies: (Kyowa Hakko, Yamanouchi, Chugai, Fujisawa Shionogi)</li> </ul>
<b>Synergies with other Abbott franchises</b>	<ul style="list-style-type: none"> <li>• Diagnostic and therapeutic antibodies</li> <li>• Tumor load testing</li> <li>• Pharmacodynamics</li> <li>• Pharmacogenomics</li> <li>• Target therapy to tumor genotype</li> </ul>	<ul style="list-style-type: none"> <li>• Fund a common discovery platform</li> <li>• In-license technology (eg Chromavision) and/or fund discovery</li> <li>• Partner/academic collaboration</li> <li>• Impath</li> </ul>

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HIGHLY CONFIDENTIAL  
ABBT006076;

**756**



**VICE PRESIDENT  
GLOBAL PHARMACEUTICAL  
DRUG DEVELOPMENT**

**INTEROFFICE  
MEMORANDUM**

**FROM: John M. Leonard, M.D.  
DEPT: 432, AP9-1  
PHONE: 847-938-4545  
FAX: 847-937-3918  
DATE: November 9, 2001**

**TO: Jeff Leiden D-3RD AP6D**

**CC: Dave Goffredo D-309 AP30  
Ed Ogunro D-87W AP30  
Bob Funck D-300 AP30  
Tom Lyons D-404 AP9  
Bryan Ford D-4FA AP9  
Gill Hodgkinson D-477 AP6A**

**RE: MONTHLY HIGHLIGHTS – OCTOBER, 2001**

**ANTI-INFECTIVE**

**ABT-492**

- FDA gave approval to start the Phase IIa Acute Bacterial Exacerbations of Chronic Bronchitis study M01-298. Shipment of drug was initiated on 10/31/01.

**ABT-773**

- The Phase I QT Study, M01-325 was put on hold at the 2nd dosing period to allow for analysis of liver elevations seen in 4 subjects. Analysis is ongoing and a discussion with FDA is planned for the first week of November to discuss modifications to this study.
- Enrollment in the M00-219 Community Acquired Pneumonia (CAP) and M00-225 Acute Bacterial Sinusitis QD vs BID studies was halted as adequate numbers of subjects were enrolled for a dose decision as well as for the collection of pathogens. An interim analysis of 400 CAP patients is planned for mid-December.
- The M00-223 Pharyngitis vs Penicillin V study final classification was completed in October. Blind breaking will take place in early November with study results available once final data queries are completed.

**ABT-268**

**REDACTED**

**HSR-903**

**ANTIVIRAL**

**ABT-378/r (Kaletra)**

October 2001 Monthly Highlights  
November 9, 2001  
Page 2 of 4

**CARDIOVASCULAR**

Propafenone SR

**REDACTED**

**IMMUNOSCIENCE**

D2E7

J695

October 2001 Monthly Highlights  
November 9, 2001  
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Segard

**REDACTED**

**NEUROSCIENCE**

ABT-089

ABT-963

BSF201640

Dilaudid OROS - EU & Canada

**ONCOLOGY**

ABT-100

- 11/2 delivery of the non-GMP material for toxicology range finding studies on schedule.

ABT-510 (TSP)

- Initiated IND study (M01-302) at Arizona Cancer Center with Dr. Dan Von Hoff on 10/23.

ABBT 0003480  
HIGHLY CONFIDENTIAL

October 2001 Monthly Highlights  
November 9, 2001  
Page 4 of 4

ABT-627

- FDA letter received by Abbott recommends that Abbott notify investigators of the potential irreversible testicular damage seen in animal reproductive data of endothelin antagonist as a class. Abbott to request from FDA additional data and information regarding the safety of single dose or short-term clinical studies.
- Atrasentan study team agrees upon fast track submission plan. Plan to be sent to FDA by November 30.
- Preliminary findings revealed no effect of atrasentan on HERG ion channels.

ABT-751

- The third patient in the MTD study M00-231 at Vanderbilt experienced a dose-limiting-toxicity (DLT) at 300 mg QD. This cohort will be expanded to 6 patients to further assess the safety of this dose. The BID dosing will not begin until this cohort is completed.

ABT-828

**REDACTED**

**UROLOGY**

ABT-724

- Held off site team meeting to solicit input from functional support areas for project timeline.

AU-224

**DRUG SAFETY**

**EUROPEAN VENTURE RESEARCH/ EUROPEAN CLINICAL OPERATIONS**

**PARD**





# **ANALGESIA VENTURE**

## **2001 PLAN**

**Revised 1/26/01**

To:

John Leonard  
Chris Silber  
George Carter  
Bruce McCarthy  
Mike Biarnesen  
Bob Funck  
Mike Higgins  
Mike Comilla  
Matt Russell  
Tom Woidat  
Barbara Massa

**Analgesia Venture  
2001 PLAN Review (Pass II)  
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Analgesia Venture  
Summary  
2001 PLAN Pass II

	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
ABT - 594	9,300	14,411	9,307	(7) a
ABT - 089	..	3,000	613	(613) b
NPS 1776	..	..	537	(537) c
ABS - 103	..	..	..	.. b
ABT - 963	..	4,000	1,186	(1,186) b
Venture Total	<u>9,300</u>	<u>21,411</u>	<u>11,643</u>	<u>(2,343)</u>

a Includes a \$120,000 charge from SPD not in Oracle

b Completion of work started in 2000, bringing it to a logical holding position.

c Includes a \$490,000 charge from SPD included in Oracle in error.



Analgesia Venture  
ABT-089  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
Neuronal nicotinic receptor modulator (Unfunded)	...	3,000	613	(613)

Key Milestones / Assumptions	00 AGU	01 PLAN	Status (on target, pending or delayed to x)
Transition Team Go/No Go		TBD	Unfunded, program on hold

PARD	00 AGU	01 PLAN
- Analytics Dev & Support	156	...
- Formulation Dev & Support	147	...
- Clinical Finishing	34	...
- Project Management Support	29	...
- PARD Total	366	...

Total Venture Management	00 AGU	01 PLAN	SPD Requirements
- Expense: \$3,564 a decrease of \$837 resulting from milestone funding (\$2,268 represents full year fixed/overhead)	156	...	Kgs Heads Martl Cost Total Cost
- Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, no headcount after July, 2001	147	...	...
	34	...	...
	29	...	...
	366	...	...

Clinical Grants	1st Patient Dosed	Last CRF	R/oss 2000 AGU	Cost
	Start	End	Start	00 AGU 01 PLAN Variance

Phase I

Total

Analgesia Venture  
NPS 1776  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

<u>Project</u>	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
NPS-1776 (Unfunded)	...	...	537	(537)

<u>Key Milestones / Assumptions</u>	00 AGU	01 PLAN 4/2001	Status (on target, pending or delayed to x)
DDC Meeting			

<u>PARD</u>	00 AGU	01 PLAN
Analytics Dev & Support		...
Formulation Dev & Support		...
Clinical Finishing		...
Project Management Support		...
PARD Total	...	...

<u>Total Venture Management</u>	<u>SPD Requirements</u>			
Expense: \$3,564 a decrease of \$837 resulting from milestone funding (\$2,268 represents full year fixed/overhead)	Kgs	Heads	Mat'l Cost	Total Cost
Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, no headcount after July, 2001	2000 AGU	...	...	...
	2001 PLAN	...	...	490

<u>Clinical Grants</u>	1st Patient Dosed	Last CRF	R/oss 2000 AGU	R/oss 2001 PLAN	Cost 00 AGU	Cost 01 PLAN	Variance
	Start	End	Start	End	Total		

Total

Analgesia Venture  
ABS-103  
2001 PLAN KEY STATISTICS Pass II  
(\$000)

Project	2001 Target	2000 AGU	2001 PLAN	Target vs PLAN Fav(Unfav) Var
ABS - 103 (Unfunded)	...	...	...	...

Key Milestones / Assumptions	00 AGU	01 PLAN 4/2001	Status (on target, pending or delayed to x)
- DDC Meeting			
-			
-			
-			
-			

PARD	00 AGU	01 PLAN
- Analytics Dev & Support	...	...
- Formulation Dev & Support	...	...
- Clinical Finishing	...	...
- Project Management Support	...	...
- PARD Total	...	...

Total Venture Management	SPD Requirements			
- Expense: \$3,564 a decrease of \$837 resulting from milestone funding (\$2,268 represents full year fixed/overhead)	Kgs	Heads	Mar'l Cost	Total Cost
- Authorized Heads: Flat to AGU until July, 2001, ABT-594, Go/No Go Decision, no headcount after July, 2001	...	...	...	...
	2000 AGU	...	...	...
	2001 PLAN	...	...	...

Clinical Grants	1st Patient Dosed	Last CRF	R/oss 2000 AGU	Cost		
	Start	End	Start	00 AGU	01 PLAN	Variance

*Phase I*

**Total**





Analgesia Venture  
CLINICAL GRANTS  
ABT-594  
2001 PLAN Pass II

CLINICAL GRANTS																		
ABT-594																		
2001 PLAN Pass II																		
2000 AGU																		
2001 PLAN																		
Study	ROSS Protocol	Patients	Start	End	Total \$	Prior	2000	Future	Grand Total	Patients	Start	End	Total \$	Prior	2001	Future	Grand Total	2001 PLAN vs 00 AGU FAV/(UNFAV)
Program Phase I:																		(165,000)
Human Metabolism 3H	M98-971																	(300,000)
GRU/human pain model																		(500,000)
Titration Optimization																		
Phase IIb:																		(100,000)
Neuropathic Pain (Diabetic)	107608 M99-114	320	Apr-00	Nov-00	3,000,000		3,000,000											
Phase III:																		
BLUE PLAN																		
Chronic Persistent Pain Publication																		(3,507,333)
Back out Blue Plan Studies																		3,507,333
Adjustments																		
Back out Clin Pharm Studies																		
																		(1,065,000)



[illegible]

Analgesia Venture  
CLINICAL GRANTS  
ABS-103  
2001 PLAN Pass II

Study	ROSS	Protocol	2000 AGU					2001 PLAN					2001 PLAN vs 00 AGU FAV/(UNFAV) \$
			Patients	Start	End	Total \$	Prior	2001	Future	Grand Total			
Program Phase I:													
Phase IIb:													
Phase III:													
Blue Plan Single Rising Dose Back out Blue Plan					48 Oct-00 Jan-02	525,000 (525,000)		394,000 (394,000)	131,000 (131,000)	525,000 (525,000)		(394,000) 394,000	
Adjustments: Back out Clin Pharm Studies													
TOTAL													

Discovery  
CLINICAL GRANTS  
ABT-963  
2001 PLAN Pass II

Study	ROSS Protocol	2000 AGU					2001 PLAN					2001 PLAN vs 00 AGU FAV/(UNFAV) \$		
		Patients	Start	End	Total \$	Prior	2001	Future	Grand Total	Total \$	Prior	2001	Future	Total
Program Phase I: Single Rising Dose EU		48	Nov-00	Feb-01	261,390	130,695	130,695		261,390		156,834	104,556		261,390
Phase II:														
Phase III:														
Blue Plan Mult Rising Dose Dental Pain Back out Blue Plan Studies		48 280	Mar-01 Mar-01	Jun-01 Jun-01	361,000 700,000 (1,061,000)		361,000 700,000 (1,061,000)		361,000 700,000 (1,061,000)					361,000 700,000 (1,061,000)
Adjustments: Back out Clin Pharm Studies														
TOTAL					261,390	130,695	130,695	...	261,390		156,834	104,556	...	261,390

**Analgesia Venture  
2001 PLAN  
\$(000)**

2000 Actual	EXPENSE	2001 PLAN			
		2000 AGU	Head Count Chgs	Other Activity	% fav(unfav)
1,172.6	Net Payroll	1,099.4	(41.3)	..	103.8%
99.7	Scientific Professionals	98.1	(4.0)	(0.8)	104.9%
124.8	Travel and Entertainment	152.7	..	125.3	17.9%
52.7	Other Employee Related	54.4	..	29.8	45.2%
0.1	Clinical Supplies	..	..	..	N/A
18.2	Case Report Forms	17.1	..	8.2	52.0%
223.5	Consultantship/Honorariums	160.5	..	97.8	39.1%
..	HPD Project Charges	..	..	(4,028.0)	4,028.0
462.5	Other Operating	461.5	..	338.5	26.7%
203.7	Fixed Expenses	203.7	..	(26.3)	-112.9%
2,357.8	Total Functional Expense	2,247.4	(45.3)	(3,454.7)	255.8%
2,154.0	Overhead	2,154.0	..	(114.0)	-105.3%
4,511.8	Gross Expense	4,401.4	(45.3)	(3,568.7)	182.1%

Hydrocodone/Bupropion

1/01	3/01	6/01	9/01	12/01
6	6	6	6	..
5	5	5	5	..
11	11	11	11	..
2	2	2	2	..
1	1	1	1	..
14	14	14	14	..
4	4	4	4	..
18	18	18	18	..

2000 Actual	HEADCOUNT	Y/E Authorized	
		2000 AGU	2001 PLAN
6	EXEMPT	7	..
5	NON-EXEMPT	6	..
11	TOTAL REGULAR	13	..
2	SCIENTIFIC PROFESSIONALS	1	..
1	CONTRACTS	..	..
14	TEMPS	..	..
14	Sub Total	14	..
..	UNFILLS	2	..
14	Total Authorized Headcount	16	..

\* Payroll/Fringe for the full year, assuming Neurophatic Pain is funded \$1,466.7 (Includes addition of 4 exempt, 1 non exempt and 1 Sci/Pro Head)  
 \* Payroll/Fringe for the full year, for current Abbott Employees \$1,109.2

26-Feb-05

06:11 PM

curr ex	663,328.0
promo	7,296.6
total pay	670,624.6
fringe	236,059.9
tl fring/pay	906,684.5
curr not ex	144,556.0
promo	1,445.6
total pay	146,001.6
fringe	56,502.6
tl fring/pay	202,504.2
	1,109,188.6

**Analgesia Calendarized Headcount  
2001 PLAN Pass II**

Name	Title	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
<b>Budgeted</b>													
<b>Abbott</b>													
Biarnesen	Ops Mgr	1	1	1	1	1	1	1					
Collicot	CPM	1	1	1	1	1	1	1					
Matalonis	Pharmacist	1	1	1	1	1	1	1					
McCarthy	Med Director	1	1	1	1	1	1	1					
O'Neill	CPM	1	1	1	1	1	1	1					
Silber	Venture Head	1	1	1	1	1	1	1					
Feige	Clin Admin	1	1	1	1	1	1	1					
Kacos	Clin Admin	1	1	1	1	1	1	1					
Morales	Clin Admin	1	1	1	1	1	1	1					
Palbicke	Admin Assit	1	1	1	1	1	1	1					
Perri	Clin Admin	1	1	1	1	1	1	1					
		11	11	11	11	11	11	11					
													\$647.8
<b>Contractor</b>													
Sweetwood	Secretary	1	1	1	1	1	1	1					
													\$18.0
<b>Sci/Pro</b>													
Borgstrom	Sci/Pro												
Davis	Sci/Pro												
Christensen	Sci/Pro												
Blake-Michaels	Sci/Pro												
Total Equivalent Headcount		2	2	2	2	2	2	2					\$102.9
Total Headcount		14	14	14	14	14	14	14					\$768.7



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	52
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<b>Contractor</b>	Judy	Secretary	1	1	1	1	1	1	1	1	1	1	\$31.8
Sweetwood													
<b>Sci/Pro</b>	Marian	Sci/Pro											
Borgstrom	Jan	Sci/Pro											
Davis	Phyllis	Sci/Pro											
Christensen	Molly	Sci/Pro (thru June)											
Blake-Michaels		Sci/Pro (start Oct)											
Pharmacist		Sci/Pro (start Sept)											
Pharmacist													
Total Equivalent Headcount			2	2	2	2	2	2	2	2	3	3	\$220.4
Total Headcount			14	14	14	14	14	14	14	18	19	20	\$1,466.7

## Blue Plan Summaries

ABT 594 ABT 594 ABT 089 ABS 103 NPS 1776 ABT 963  
 Milestone CPPP  
 BP 143010 BP 143014 BP 143100 BP 121200 BP 121100 BP 414030

Payroll	698						
Other Functionals	376						
Grants		5,261	1,628	525	1,817	1,061	
Investigational Drug							
Discovery	51		859	949	154		
Drug Safety	853	701	2,172	1,600	1,335	1,837	
PARD	2,815		1,042	840	1,840	1,029	
Phase I Center	43	22	157	193	254	529	
Development Ops	235	271	340	123	335	590	
RA/QA	22	22	17	19	69	65	
Medical Affairs			55	33	39	138	
Admin			70				
SPD	970						
Milestone Payment				1,000			

Total	6,063	6,277	6,340	5,282	5,843	5,249
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	A	B	C	D	D	F
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A	Neuropathic Pain Study completion and gear up for Phase III to support current filing target.
B	Maximize spill over in Neuropathic pain use.
C	Transition funding to achieve first go/no go milestone. Determine formulation feasibility and tox work for both adults and children.
D	Initiation of Phase I studies
E	End of Phase I milestone, safety PK and formulation requirements
F	Phase I multi does and 3 month safety studies in two species.

Payroll for full year 2001, assuming only Neuropathic Pain is funded																									
2001 PLAN																									
DBPT-48Q-Exempt Payroll																									
SSN	Name	Job Title	Effective Dates		Grade	Est Monthly Salary	Est Monthly Salary	Actual Increase %	Actual Increase Date	Salary After Increase	Annual Salary After Increase	Total	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
1 348-40-3041	Birnussen	Mike	Ops Mgr	01/01/01	12/31/01		8,951.21	8,951.21	4.0%	11/15/01	9,309.26	111,711.10	108,128	1	1	1	1	1	1	1	1	1	1	1	
2 398-58-5404	Colloid	Manlyn	CPM	01/01/01	12/31/01		6,334.30	6,334.30	4.0%	10/15/01	6,587.67	79,052.08	78,770	1	1	1	1	1	1	1	1	1	1	1	
3 321-40-2510	Mallionis	Aldona	Pharmacist	01/01/01	12/31/01		5,672.04	5,672.04	4.0%	10/15/01	5,899.92	70,787.08	69,745	1	1	1	1	1	1	1	1	1	1	1	
4 542-02-8238	McCarthy	Bruce	Med Director	01/01/01	12/31/01		13,191.86	13,191.86	4.0%	08/15/01	13,719.53	164,634.41	160,944	1	1	1	1	1	1	1	1	1	1	1	
5 346-72-2792	O'Neill	Alyssa	Sr. CRA	01/01/01	12/31/01		4,585.11	4,585.11	4.0%	11/15/01	4,768.51	57,222.17	55,388	1	1	1	1	1	1	1	1	1	1	1	
6 131-46-4488	Silber	Chris	Venture Head	01/01/01	12/31/01		15,643.57	15,643.57	4.0%	04/15/01	16,269.31	195,231.75	183,353	1	1	1	1	1	1	1	1	1	1	1	
OPEN:																									
	ABT-594 Neuro Ex-US	CPM		09/01/01	12/31/01		6,000.00	6,000.00	4.0%	09/01/02	6,240.00	74,880.00	24,000	0	0	0	0	0	0	0	0	1	1	1	
	ABT-594 Neuro US	Sr. CRA		09/01/01	12/31/01		4,400.00	4,400.00	4.0%	09/01/02	4,576.00	54,912.00	17,800	0	0	0	0	0	0	0	0	0	1	1	
	ABT-594 Phase I Studies	Sr. CRA		11/01/01	12/31/01		4,400.00	4,400.00	4.0%	11/01/02	4,576.00	54,912.00	8,800	0	0	0	0	0	0	0	0	0	1	1	
	ABT-594 Neuro Ex-US	Sr. CRA		09/01/01	12/31/01		4,400.00	4,400.00	4.0%	09/01/02	4,576.00	54,912.00	17,800	0	0	0	0	0	0	0	0	1	1	1	
Sub Total Regular												731,328													
PART TIME:																									
				01/01/01	12/31/01				4.0%	01/01/01	0.00	0.00	0	0	0	0	0	0	0	0	0	0	0	0	
Sub Total Part Time:																									
INTERNS:																									
Sub Total Interns:																									
													INTERNS NOT INCLUDED												

9.11.19

Payroll for full year 2001, assuming only Neuropathic Pain is funded.									
	Name	Company	Hours	Rate	Cost	Hours/week	Equivalent As a group		
D05148Q	Borgstrom Marian	Trilogy Consulting	832	54.00	44,928	16 Hours/week	44,928		
	Davis Jan	L Jan Davis	1,248	27.50	34,320	24 Hours/week	34,320		
	Christensen Phyllis		1,960	54.00	84,240	30 Hours/week	84,240		
	Blake-Michael Molly		130	66.00	8,580	5 Hours/week (thru June)	8,580		
	Pharmacist ABT 594 Neuro Ex US		2,080	29.50	61,360	40 Hours/week Starting in Oct	16,520		
	Pharmacist ABT 594 Neuro US		2,080	28.50	30,880	40 Hours/week Starting in Sept	31,860		
TOTAL			7,930		\$284,108		220,448		
Equivalent Headcount calculation					2.4		2.0		
D05148Q	Sweetwood Judy	Manpower	2,080	15.00	31,200	40 Hours/week	31,800		
							0		
							0		
	TOTAL		2,080		\$31,200		31,800		
Equivalent Headcount calculation					0.8		9.5		

Payroll for all current employees thru July and August through year end																								
2001 PLAN																								
2001 PLAN																								
SSN	Name	Job Title	Effective Dates	Grade	Est Monthly Salary @ 12/31/2000	Actual Increase %	Actual Increase Date	Salary After Increase	Annual Salary After Increase	Total	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec		
1 388-58-5404	Collicot	CPM	01/01/01 12/31/01		6,334.29	4.0%	10/15/01	6,587.68	79,051.94	76,770	1	1	1	1	1	1	1	1	1	1	1	1		
2 542-02-8238	McCarthy	Med Director	01/01/01 12/31/01		13,181.85	4.0%	08/15/01	13,719.52	164,634.29	160,944	1	1	1	1	1	1	1	1	1	1	1	1		
3 131-46-4489	Silber	Venture Head	01/01/01 12/31/01		15,843.57	4.0%	04/15/01	16,269.31	195,231.75	193,353	1	1	1	1	1	1	1	1	1	1	1	1		
4 321-40-2510	Merlonis	Pharmacist	01/01/01 12/31/01		6,182.02	4.0%	10/15/01	6,429.30	77,151.61	74,925	1	1	1	1	1	1	1	1	1	1	1	1		
5 348-40-3041	Barnesen	Ops Mgr	01/01/01 12/31/01		8,951.21	4.0%	11/15/01	9,309.26	111,711.10	108,128	1	1	1	1	1	1	1	1	1	1	1	1		
6 348-72-2792	O'Neill	Sr CRA	01/01/01 12/31/01		4,585.11	4.0%	11/15/01	4,768.51	57,222.17	55,388	1	1	1	1	1	1	1	1	1	1	1	1		
OPEN:		CPM						0.00	0.00	0	0	0	0	0	0	0	0	0	0	0	0	0		
		Sr CRA																						
		Sr CRA								689,508														
Sub Total Regular											0	0	0	0	0	0	0	0	0	0	0	0		
PART TIME:																								
			01/01/01 12/31/01			4.0%	01/01/01																	
Sub Total Part time:																								
INTERNS:																								
									0.00	0.00														
Sub Total Interns:											6	6	6	6	6	6	6	6	6	6	6	6		
									Example Payroll	669,508														
									Promotions =	1.1%	6,695													
									Turnover =	0.0%	0													
									Fringe Rate =	35.2%	238,023													
									Total		914,226													

INTERNS NOT INCLUDED





Payroll for all current employees thru July and Abbott through year end										
Dept 4801 - Support										
Name	Company	Hours	Rate	Cost	Hours/week	Hours/week	Hours/week	Hours/week	Hours/week	Equivalent As a group
Borgstrom	Manan	832	54.00	44,928	16	Hours/week				25,920
Davis	L Jan Davis	1,248	27.50	34,320	24	Hours/week				19,800
Christensen	Phyllis	1,550	54.00	84,240	30	Hours/week				48,600
Blake-Michael	Molly	130	66.00	8,580	5	Hours/week (thru June)				8,580
Open Pharmacist		2,080	29.50	30,680	40	Hours/week Starting in July				0
TOTAL		5,850		\$202,748						102,800
Equivalent Headcount calculation				1.8						11.1
Dept 4802 - Contractors										
Sweetwood	Judy	2,080	15.00	31,200	40	Hours/week				18,000
TOTAL		2,080		\$31,200						0
Equivalent Headcount calculation				0.8						5.4



Payroll thru July supporting ABT-S94 Only																								
2001 PLAN		Dept 4402 - Example Payroll 2002																						
SSN	Name	Job Title	Effective Dates		Grade	Est Monthly Salary @ 12/31/2000	Increase %	Actual Increase Date	Salary After Increase	Annual Salary After Increase	Total	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
1 388-58-4404 Colton	Mathyn	CPM	01/01/01	07/31/01		8,334.29	4.0%	10/15/01	6,587.66	79,051.94	44,338	1	1	1	1	1	1	1	1	0	0	0	0	
2 542-02-8238 McCarty	Bruce	Med Director	01/01/01	07/31/01		13,181.85	4.0%	08/15/01	13,719.52	164,834.28	92,344	1	1	1	1	1	1	1	1	0	0	0	0	
3 131-48-4489 Silber	Chris	Venture Head	01/01/01	07/31/01		15,643.57	4.0%	04/15/01	16,289.31	195,231.75	112,008	1	1	1	1	1	1	1	1	0	0	0	0	
4 321-40-2510 Mikalonia	Audena	Pharmacist	01/01/01	07/31/01		6,182.02	4.0%	10/15/01	6,428.30	77,151.61	43,274	1	1	1	1	1	1	1	1	0	0	0	0	
5 348-40-3041 Blumstein	Mike	Ops Mgr	01/01/01	07/31/01		8,951.21	4.0%	11/15/01	9,309.29	111,711.10	62,857	1	1	1	1	1	1	1	1	0	0	0	0	
6 348-72-2192 ONeil	Alyssa	Sr CRA	01/01/01	07/31/01		4,585.11	4.0%	11/15/01	4,768.51	57,222.17	32,095	1	1	1	1	1	1	1	1	0	0	0	0	
OPEN:		CPM							0.00	0.00	0	0	0	0	0	0	0	0	0	0	0	0	0	
		Sr CRA																						
		Sr CRA									388,716													
Sub Total Regular																								
PART TIME:				01/01/01	12/31/01		4.0%	01/01/01	0.00	0.00	0	0	0	0	0	0	0	0	0	0	0	0	0	
Sub Total Part time:																								
INTERNS:																								
Sub Total Interns:												6	6	6	6	6	6	6	6	0	0	0	0	
									Exempt Payroll		388,716													
									Promotions =	1.1%	3,867													
									Turnover =	0.0%	0													
									Fringe Rate =	35.2%	137,485													
									Total		528,688													

INTERNS NOT INCLUDED

Payroll thru July supporting ABT-354 Only										HEADCOUNT													
SSN	Name	Job Title	Effective Dates		Grade	Est. 12/31/2000 Hourly Rate	Increase %	Increase Date	Rate After Increase	Annual Salary After Increase	Total	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
			Start	End																			
DATA FOR Non-Exempt Payroll																							
REGULAR:																							
1 058-60-3324	Morales Ray	Clin Resch Admin	01/01/01	07/31/01		15.80	4.0%	09/15/01	16.43	33,028.32	18,455	1	1	1	1	1	1	1	1	0	0	0	0
2 325-44-8951	Felton Carol	Clin Resch Admin	01/01/01	07/31/01		14.30	4.0%	11/15/01	14.87	29,892.72	14,413	1	1	1	1	1	1	1	1	0	0	0	0
3 327-70-2850	Kecoa Cathy	Clin Resch Admin	01/01/01	07/31/01		17.11	4.0%	01/15/01	17.78	35,766.74	17,934	1	1	1	1	1	1	1	1	0	0	0	0
4 356-28-0258	Pellick Nancy	Admin Asst	01/01/01	07/31/01		18.68	4.0%	09/15/01	19.75	39,696.70	19,145	1	1	1	1	1	1	1	1	0	0	0	0
5 398-78-8954	Perri Joan	Clin Resch Admin	01/01/01	07/31/01		13.30	4.0%	09/15/01	13.83	27,802.32	13,405	1	1	1	1	1	1	1	1	0	0	0	0
Sub Total Regulars											81,352												
PART TIME:																							
Sub Total Part time:											0												
TEMP:																							
Sub Total Temp:											0.00												
Non-Exempt Payroll											81,352												
Promotions =											2,100												
Leaves =											833												
Fringe Rate =											33,393												
Total											119,878												

Payroll thru July supporting ABT-394 Only											
Dept 480 - SCUP TOB											
Name	Company	Hours	Rate	Cost	16 Hours/Week	24 Hours/Week	30 Hours/Week	5 Hours/Week (thru June)	40 Hours/Week Starting in July	Equivalent As a group	
Borgstrom	Trisopt Consulting	832	54.00	44,928						25,920	
Devis	L. Jan Davis	1,248	27.50	34,320						19,800	
Christensen	Phyllis	1,560	54.00	84,240						48,600	
Black-Mohr Mully		130	66.00	8,580						8,580	
Open Pharmacist		2,080	29.50	39,680						0	
TOTAL		5,850		\$202,748						102,900	
Equivalent Headcount calculation				1.8						11.1	
Dept 480 - Contract 1975483											
Sweetwood Judy	Mampower	2,040	15.00	31,200	40 Hours/Week					18,000	
TOTAL		2,040		\$31,200						0	
Equivalent Headcount calculation				0.6						5.4	

**760**



**From the Office of the Executive V.P. Pharmaceuticals & Chief Scientific Officer**

*Jeffrey M. Leiden, M.D., Ph.D.*

To: M. Beatrice  
C. Begley  
B. Dempsey  
D. Golfredo  
R. Gonzalez  
M. Heath-Chiozzi  
B. Kamen  
J. Leonard  
D. Norbeck  
E. Ogunro  
J. Tyree  
S. Weger  
L. Wyatt

cc: J. Arnott  
B. Ford  
S. Bukofzer  
S. Nibhuachalla  
E. Sun  
J. Wenker

Re: Summary of 12/10/01 PEC Meeting

The December 10 PEMC meeting focus was on the anti-infective franchise with specific discussions on ABT-773 and ABT-492. Jerry Wenker's and John Arnott's teams prepared a thorough analysis of the current development status of each of the noted products. The following decisions were made by the PEC:

**ABT-773**

- The project should be put on hold. Do not start any new studies or activities. Existing studies and projects should be continued.
- Jim Tyree will aggressively pursue out-licensing or selling the compound.

- The team is to prepare a 30 minute presentation for Miles White which summarizes the issues and presents the recommendations. The meeting should take place in December 2001.

- 

#### ABT-492

- The team is to generate a product profile for the compound which defines the performance parameters for commercial success.
- A Phase II program should be designed to stress the defined profile parameters.
- Do not start additional, Phase II studies until approved by PEC

#### Other

- Funding was not authorized for the ketolide backup compounds discussed.
- Jim Tyree will aggressively pursue licensing/acquisition rights to Gatifloxacin

#### Future PEMC Agenda Items

- January Meeting
  - Review Omnicef R/D spending against the product profitability and present alternatives.

#### February Meeting

- Review the Clari life-cycle management opportunities.
- Review the Pump Inhibitor Program status.





From: Jeff Leiden  
John Leonard

INTEROFFICE CORRESPONDENCE

TO: Miles White

Date: Jan. 7, 2002

CC:

Bill Dempsey  
Dave Goffredo  
Mary Szela  
Jim Tyree  
Eugene Sun  
Stan Bukofzer

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**RE:**

On December 10<sup>th</sup>, the Pharmaceutical Executive Committee met to review the development status of ABT-773, our ketolide antibiotic in clinical development for respiratory tract infections. Based on the data reviewed at the meeting, the Committee recommends suspending further development and initiating efforts to out license the compound. Attached is a package, which addresses the key issues. Our decision for this recommendation is based on the following:

**1. Divergence from the target product profile**

ABT-773 was approved for clinical development in a March 1997 Drug Development Committee (PPCC), at which time the key elements of the target product profile were defined as:

- ◆ Once daily dosing for short course treatment regimens (5-10 days)
- ◆ Favorable side effect profile relative to currently available therapies
- ◆ Efficacy against major respiratory pathogens, particularly against resistant organisms, a key differentiating feature of this compound
- ◆ Once daily dosing has not been achieved in 3 of 4 respiratory indications:
  - ◆ In July 2001, twice daily dosing was chosen for the pivotal Phase III clinical trials in sinusitis and community acquired pneumonia. This decision was taken based on accumulated scientific data and to enhance regulatory approvability of the compound, but recognized a corresponding decrease in the commercial value; particularly given the global trend toward once-a-day/shorter course therapy.
  - ◆ In November, the pivotal U.S. Phase III trial in pharyngitis showed that ABT-773 dosed once daily at the chosen dose had insufficient efficacy for approval. Additionally, these results cast some doubt on the potential for QD dosing for bronchitis.



- ◆ The emerging side effect profile of ABT-773 is neither significantly better nor worse than clarithromycin in terms of taste and the potential for drug-drug interactions. There are still safety issues that remain to be better defined, i.e., the potential for QT prolongation, and the incidence and severity of liver enzyme abnormalities (see #3 below).
- ◆ A resistance claim, which is a key point of commercial differentiation, will be challenging to achieve:
  - ◆ The resistance claim is based on successful treatment of pneumonia patients who have resistant organisms. The original ABT-773 plan targeted approximately 15 such patients. In 2001, the EMEA and FDA evaluated telithromycin (Ketek), Aventis' first-in-class ketolide. Neither the EMEA nor FDA considered the Ketek data sufficient to support a resistance claim based on 17 patients with about an 85% eradication rate. It is now anticipated that a resistance claim for ABT-773 will require a larger number of resistant isolates (this requirement will significantly increase the size, complexity, and duration of clinical trials) as well as an eradication rate of at least 85%.

## 2. Increasing regulatory stringency

- ◆ Regulatory approval of new antibiotics is increasingly dependent on their benefit:risk ratio compared to currently available therapies. Given that most respiratory antibiotics have greater than 85% success rates there is increasing attention to drug safety. Although Ketek was approved by EMEA this year, significant post approval commitments were mandated, i.e., additional safety data in over 4000 patients. In the US, Aventis has been asked to obtain additional safety data prior to FDA approval. Given that some of the same safety issues may apply to ABT-773, the projected size of the required safety database for ABT-773 has increased considerably. This will increase the expense and duration of the phase III trials.
- ◆ Regulatory authorities are increasingly concerned about widespread antibiotic resistance resulting from inappropriate antibiotic usage. They are considering ways to curb indiscriminate antibiotic usage, such as limiting regulatory approval for indications that do not always warrant antibiotic therapy, e.g., acute exacerbation of chronic bronchitis. This indication represents one of the largest respiratory market segments.

## 3. Unresolved potential safety issues

- ◆ QT prolongation by ABT-773 has not been fully characterized and remains a potential liability. In recent years, broad regulatory attention to this issue has resulted in increasing requirements for *in vitro* as well as clinical data to assess this risk. To date, data indicates that QT prolongation by ABT-773 is comparable to that of clarithromycin and Ketek, but FDA has requested additional studies. Should these studies suggest clinically significant risk, regulatory actions could include non-approval, Black Box warning, or contraindication in at-risk populations.

- ◆ Significant liver enzyme elevations have been observed in a few subjects in clinical trials to date, most recently in a study to evaluate QT prolongation. Clinical protocols have been modified to increase patient monitoring, leading to increased clinical costs and a delay in filing. Although the incidence and severity of these findings fall within an acceptable range for antibiotics, future findings may drive the requirement for a larger safety database.

#### 4. Decreased commercial valuation

- ◆ The loss of the pharyngitis indication is forecasted to erode more than \$117MM in NPV from ABT-773 (-\$82MM AI; -\$35MM PPD). Based on the above information, the global NPV of ABT-773 falls from a July 2001 \$223MM to \$51MM with the U.S. market NPV largely break-even at \$3MM and Abbott International contributing the balance of value.
- ◆ In addition, if the regulatory authorities require additional patients to evaluate safety, the value of ABT-773 becomes negative.

Attached are several slides that provide additional detail to the issues discussed above. Obviously we are extremely disappointed to recommend stopping a key phase III program in development. However, at this time, the team recommends placing development on hold and redirecting R & D funds to higher return opportunities. If this decision is made shortly, the team forecasts that it would create a 2002 R&D favorability of approximately \$47MM.

#### Next Steps

We look forward to meet with you regarding our recommendation and to secure your approval to move forward with the decision to place clinical development on hold. If approved, the next steps will include:

- ◆ The preparation of an internal and external communication package for all stakeholders paying particular attention to PR issues and timing of the process.
- ◆ Communicating with Taisho. As you are aware, the development of ABT-773 has been conducted in collaboration with Taisho under a 1997 Agreement in which Taisho contributes 50% of the Japanese development cost and 10.69% of the ex-Japan expenses. Abbott has the right to out license the compound outside Japan without Taisho's consent, but the royalty obligations remain in effect (5.5% in patented territories and 2.75% in non-patented countries). Sub-licensing of Abbott's rights in Japan is allowed only after Taisho's consent.
- ◆ The PLC believes that the compound may hold potential for out licensing. To capture value for ABT-773 an out licensing effort, which might include follow-on compounds already in discovery, would be aggressively initiated.



**MEMORANDUM OF MEETING MINUTES**

**Meeting Date:** November 27, 2000  
**Location:** CORP S-300  
**Application:** IND 57,836  
**Drug:** ABT-773  
**Type of Meeting:** End of Phase 2 Meeting  
**Meeting Chair:** Dr. Janice Soreth, M.D., Acting Division Director

**FDA's Attendees:**

Mercedes Albuerne, M.D., Medical Team Leader  
Nasim Moledina, M.D., Medical Officer  
Mamodikoe Makhene, M.D., Medical Officer  
Alma Davidson, M.D., Medical Officer  
Daphne Lin, Ph.D., Statistics Team Leader  
Erica Brittain, Ph.D., Statistics Reviewer  
Terry Peters, D.V.M., Veterinary Medical Officer  
Robert Osterberg, Ph.D., Pharm/Tox Team Leader  
Lilian Gavrilovich, M.D., Deputy Director  
Charles Bonapace, PharmD, Biopharmaceutics Reviewer  
Frank Pelsor, PharmD, Biopharmaceutics Team Leader  
Sousan Altaie, Ph.D., Microbiology Reviewer  
Jean Mulinde, M.D., Medical Officer  
Jim Timper, Chemistry, Reviewer  
Charles Cooper, M.D., Medical Officer  
Albert Sheldon, Ph.D., Microbiology Team Leader  
Janice Soreth, M.D., Acting Division Director  
John Alexander, M.D., Medical Officer  
Diane Murphy, M.D., Office Director ODEIV

**Abbott Representatives:**

Greg Bosco, Sr. Product Manager, Regulatory Affairs  
Jeanne Fox, Director Regulatory Affairs  
Jie Zhang, Statistician Clinical Statistics  
Joaquin Valdes, Physician Anti-Infective Venture  
Carol Meyer, Operations Manager Anti-Infective Venture  
Bob Flamm, Microbiologist Microbiology  
Linda Gustavson, Pharmacokineticist Clinical Pharmacokinetics  
David Morris, Statistician Clinical Statistics  
Maria Paris, Physician Anti-Infective Venture  
George Aynilian, Associate Venture Head Anti-Infective Venture  
Carl Craft, Venture Head Anti-Infective Venture  
John Leonard, Vice President Research & Development  
Reid Patterson, Vice President Drug Safety

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AUDIT 002817**

IND 57,836  
 ABT-773  
 EOP 2 Clinical  
 Page 2

**Objective:**

The objectives of the meeting were to discuss Abbott's clinical developmental plan for ABT-773 oral tablet, discuss potential issues, and address any questions regarding Phase 2 study results and future Phase 3 studies.

**Executive Summary/Background:**

A new class of antibiotics, the ketolides, has been found to be active *in vitro* against penicillin-resistant and macrolide-resistant *S. pneumoniae*. Abbott is currently developing a new ketolide antibiotic, ABT-773, in oral tablet, oral suspension, and intravenous formulations. Several Phase 2 studies have been completed using the oral tablets. The intravenous and pediatric programs are at an earlier phase of development. ABT-773 possesses broad-spectrum antibacterial activity against gram-positive and gram-negative bacteria.

Below are the proposed indications and treatment durations that Abbott is seeking:

- Community-Acquired Pneumonia (CAP) 10 Days
- Acute Bacterial Sinusitis (ABS) 10 Days
- Acute Bacterial Exacerbation of Chronic Bronchitis (AECB) 5 Days
- Tonsillopharyngitis 5 Days

Abbott will also be seeking additional claims to include the treatment of penicillin-resistant *Streptococcus pneumoniae*, macrolide-resistant *Streptococcus pneumoniae*, and atypical pathogens to include *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* in the above mentioned indications.

There has been concern regarding the potential for certain classes of antimicrobials (including macrolides and quinolones) to cause QT prolongation. ABT-773 is structurally derived from macrolides.

**ISSUES AND QUESTIONS TO THE FDA: Discussion and Recommendations**

Abbott is seeking comments on the following issues:

1. Abbott believes the scope of the clinical program in terms of number and geographical locations of clinical trials is sufficient to support the proposed indications.

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2. Abbott believes that the trial designs and statistical assumptions follow current FDA guidance documents and are adequate to demonstrate efficacy and safety of this compound.
3. Abbott believes that 15 isolates worldwide are appropriate to claim efficacy for infections caused by penicillin-resistant and macrolide-resistant *S. pneumoniae*.
4. Pediatric Deferral Waiver: Abbott is requesting a deferred submission for ABT-773 pediatric NDA.
5. ECG Monitoring plans for Phase 3.
6. Drug Interactions: At the time of filing, Abbott will have conducted or is planning to conduct drug interaction studies with oral contraceptives, theophylline, ketoconazole, rifampin, midazolam, warfarin and digoxin. Abbott believes this to be an adequate program to characterize the metabolism/interaction potential of ABT-773.

**Discussion and Recommendations:**

- Dr. Soreth began the meeting by clarifying that the ABT-773 program is **NOT** on clinical hold.
- The sponsor stated that the objectives of the studies were to select a dose for the large, well-controlled, comparative, pivotal studies, and to meet the specific pathogen criteria as required for the supportive trial in the FDA guidance for CAP and ABS. It was stressed to FDA that Abbott still intends to conduct a large, well-controlled, double-blind, comparative trial for each of these indications. The FDA advised the sponsor that there might be a problem using Augmentin 875 mg BID for the sinusitis trial and suggested the use of 500-mg TID instead. Abbott should provide the results from these two trials to FDA for review.
- Dr. Craft presented Abbott's intention to request a claim for macrolide-resistant and penicillin-resistant bacteria and atypical bacteria, and the supporting data they propose to support these claims. Dr. Albuerne stated that the sponsor could not pool isolated for ABS with those for CAP or ABECB. (Abbott proposed pooling from all three).
- Dr. Soreth mentioned that to grant a claim in CAP for PRSP, the Division recommends that the majority of the data needs to be in patients with well-documented pneumonia, including some (CAP) patients with bacteremia. The Divisions (DAIDP and DSPIDP) don't allow pooling PRSP isolates in CAP and AECB in order to support a PRSP claim in CAP. At this time, we do not allow a PRSP claim in ABECB.

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- Dr. Soreth stated that there is currently no guidance document available addressing specific requirements for resistant claims but mentioned that there are data from other products (e.g., levofloxacin) that are available in the public domain.
- Abbott's requested information on the number of PRSP isolates required. More than ten PRSP isolates in CAP could be acceptable with good data for susceptible pathogens. There has been an instance (Zyvox) where less than ten was not approved. In that case only one or two patients had bacteremia and responded well to therapy. Dr. Soreth stated that a number of bacteremic patients would be required in order to adequately evaluate clinical success against penicillin-resistant *Streptococcus pneumoniae* (PRSP). The comment was made that with oral therapy alone, Abbott would probably be hard pressed to find enough patients with bacteremia, that IV/oral therapy gave a better chance. Dr. Soreth stated that FDA has not seen sufficient data supporting clinical concern over "macrolide resistant *S. pneumoniae*" to grant this indication. She commented that she is also unaware of a good body of evidence supporting macrolide resistant *S. pyogenes* in the tonsillopharyngitis indication.
- The Sponsor proposed that ECG's would be performed in five of the six studies. In total, Abbott would be gathering ECG data on 2000 subjects exposed to ABT-773. ECGs will be performed pre-therapy, during therapy, and post-therapy. Additionally, the timing of the ECG and the timing of the dose before the ECG will be documented. Dr. Soreth recommended that a cardiologist interpret all ECGs.
- Dr. Soreth requested that Abbott amend all informed consents forms to mention possible effects on cardiac repolarization caused by ABT-773. Various examples of wording were then discussed and Abbott agreed to amend the informed consent forms for all IND studies. Dr. Soreth asked why ECGs were not being done in the sixth study. Dr. Craft stated that the European pharyngitis study would not include ECGs based on recommendations of European advisors. Subjects would probably be reluctant to participate in a trial requiring so many visits. Dr. Soreth strongly disagreed with this rationale. Dr. Murphy expressed concern that ECGs were not included in this trial, since they were included in all other studies.
- Dr. Alexander suggested the collection of a blood sample during therapy in addition to ECGs to look at ABT-773 levels and electrolytes, calcium, and magnesium.
- Dr. Peters requested additional data in the dog model. The sponsor claimed they have attempted to use the dog model in the past, but they were unsuccessful in obtaining good results. Dr. Peters stated that the monkey model is not sensitive to the QTc prolongation effect. The FDA is stressing the importance of conducting pre-clinical trials in the more sensitive animal model. The requested study should be a two-week repeat dose study with telemetry, which can run concurrent with the Phase 3 clinical trials. Dr. Patterson indicated that the emetic activity of ABT-773 in the unanesthetized dog limits exposure in this species, leading to Abbott's selection of the

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cynomolgus monkey as the non-rodent model. While the primate did not indicate a risk for QTc prolongation, exposures of 17x the human  $C_{max}$  in anesthetized dogs did lead to some prolongation. Perhaps due to the differences in protein binding, the dog reaches about 3 times the amount of unbound drug compared to the human with identical exposures, potentially expanding the margin of safety. Various proposals for the study were discussed between Dr. Patterson and Drs. Peters and Osterberg. Abbott committed to sending draft protocols to Dr. Peters for review.

- Dr. Soreth informed the sponsor that the Division has begun to ask for special population studies with drugs that show an effect on ECGs. The Division would be evaluating whether a study in otherwise healthy subjects with underlying cardiovascular disease is warranted. She commented that only looking at the effects of ABT-773 in comparator trials might not be realistic, other sponsors have been asked to conduct these types of studies.
- Dr. Murphy commented that it was in the best interests of both the FDA and Abbott to get all the information that show how to use the drug safely.
- The rest of the meeting was spent addressing specific questions regarding the four Phase 3 protocols (CAP, ABS, ABECB & tonsillopharyngitis).

#### **Community Acquired Pneumonia (CAP) Dr. Alexander**

##### **Inclusion/Exclusion Criteria**

1. **Exclusion of patients >65 years of age** - Older patients are excluded from this trial, though no specific reasons for exclusion are provided. Older patients should be studied in the comparative trials, if not included in this trial. Exclusion of geriatric patients from all CAP trials would lead to restrictive labeling for CAP in this age group.
2. **Rhonchi and wheezes in auscultatory findings** - Rhonchi and wheezes, in the absence of other auscultatory findings (rales, decreased breath sounds), can be noted in subjects who do not have pneumonia. Recording rhonchi and wheezes at baseline is acceptable, since X-ray is used to confirm the diagnosis of CAP. However, the presence of rhonchi and/or wheezes at the test-of-cure visit may complicate the clinical outcome assessment, in the absence of clear outcome definitions for improvement.
3. **Oral Contraceptive Use** - Barrier methods should be recommended for women, including using oral contraceptives.

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4. **Addition of theophylline to list of closely monitored drugs** - Theophylline should be included in the exclusion criteria as a drug that should not be used unless carefully monitored.

#### **Study Procedures**

1. **Gram Stain** - Sampling error and reading error have resulted in discrepancies between assessment of an adequate gram stain by the investigator and the central lab. Discrepant results have been noted in up to 30% of patients in other trials submitted to FDA. The investigator and the central lab should read the same slide to eliminate sampling errors. A pull slide method should be used to prepare the slide to be read by the investigator and lab, and a second slide to be used if the first slide is damaged in shipping. The central lab results should be used to determine microbiological evaluability (i.e., an adequate sputum specimen was obtained). The investigator assessment of the gram stain can be used as an entry criterion into the CAP trial, but is not required. This method will not eliminate reading errors. The sponsor should expect that some discrepancy between the reading by the investigator and the central lab will still be present.
2. **Atypical pathogens** - Outpatient treatment of CAP due to *Legionella pneumophila* is expected to be rare. For all atypical pathogens, the culture and serology results should only be considered valid when the clinical picture is consistent with this etiology and other bacterial pathogens (especially *Streptococcus pneumoniae*) have not been identified.
3. **Timing of ECG** - The time interval between the ECG and the last dose of study drug should be recorded.
4. **Blood Sampling for drug level at time of on therapy ECG** - All patients in the uncontrolled CAP trial and uncontrolled sinusitis trial could have blood drawn for drug level. This would allow for correlation of drug level with QT prolongation in clinical trial subjects.
5. **Magnesium levels** should be drawn at baseline, during therapy and at the end of therapy, since low magnesium may affect QT. Calcium and electrolytes should be added to Day 3 blood sampling.

#### **Outcome Assessment and Analysis**

1. **Clinical outcome** - Careful definitions of "improvement in signs and symptoms" sufficient to distinguish between cure and failure should be included in the protocol. Resolution of all signs and symptoms of CAP should be the usual circumstance.

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2. **Superiority design of dose comparison trial** - The purpose of this design is solely for selection of a dose for the phase 3 controlled trial. Demonstration of superiority in the current protocol will not be taken as evidence of efficacy, since the protocol allows for interim analyses without statistical adjustment.
3. **Interim Analysis** - Formalized rules for interim analyses with appropriate statistical penalty are recommended. This would provide greater confidence in the final results of the trial, or the decision to stop enrollment in a single treatment arm.
4. **Potential for Bias** - Investigators are blinded to the dose regimen, but know that all patients will be receiving some dose of ABT-773. As such, the investigators may be biased toward assessing patients as clinical cures. The cure rates seen in this trial may be higher than those seen in subsequent controlled trials.
5. **Informed Consent** - Comments about the potential for QT prolongation and the potential for drug interaction should be added to the sections on Potential Risks and Other Medications, respectively.

**Statistician - Dr. Brittain**

1. Dr. Brittain questioned why the monitoring plans for the CAP and Sinusitis trials did not control the overall alpha level. She suggested that unless the Type I error was controlled, the results of the testing would not have a clear interpretation. She further indicated that these concerns would be outlined in the follow-up fax.
2. She emphasized that the Points-to-Consider step function approach to choice of delta, which was cited in their protocols, was no longer being used. We recommended a FIXED delta value of 10% for both equivalence trials under consideration: Pharyngitis and ABECB.
3. Dr. Brittain noted that she was unable to match the sample size cited in two protocols: Sinusitis and tonsillopharyngitis, and would provide more details in the follow-up fax.

**Biopharmaceutics - Dr. Pelsor**

1. Several immediate release formulations have been developed and the sponsor and the sponsor were reminded to demonstrate bioequivalence between the formulation used in phase 3 studies and the "to be" marketed formulation.
2. The sponsor was reminded that bioequivalence should be done during non-fasting conditions

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**Action Items from this Meeting:**

- Dr. Peters requested additional data in the dog model to be submitted to the Division. Abbott committed to sending draft protocols to Dr. Peters for review.
- Dr. Davidson requested the AE narratives for Phase 2 subjects who experienced syncope or elevated liver enzymes.

The following comments were provided to Abbott after the meeting and may or may not have been discussed at the meeting.

**AECB Indication: Dr. Mulinde**

1. Revise the protocol to instruct women using hormonal contraceptives to use an additional method of barrier contraception during the study period and for at least one month after study completion (this change should occur for all patients in all studies that are using hormonal therapy as a method of birth control).
2. Add nitrites and leukocytes to planned semi-quantitative urinalysis.
3. Add Mg<sup>+</sup> level to safety labs.
4. Either exclude patients receiving concomitant theophylline or monitor theophylline levels at each study visit and record these levels in the CRF.
5. Provide the rationale for excluding Canadian sites from Quality of Life and Resource Utilization assessments.
6. Provided the Agency with plans on how Quality of Life and Resource Utilization data will be used so that DDMAC can become involve during early Phase III planning, if appropriate.
7. Incorporate a graded method of assessing sputum purulence into the protocol (and CRF) as was done for dyspnea and sputum production.
8. Require that all chest x-rays be read by a Radiologist and include Radiologists' reports in the CRF or have all chest x-rays sent to a central Radiologist that is blinded to study treatment to be reviewed.
9. Have the sputum gram stain used by the investigator to qualify a patient for study sent to the central lab to be used to qualify sputums for culturing. (As discussed in the End-of-Phase II meeting, the Division recommends

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making two "pulled" slides. The one used by the Investigator to qualify a patient for study should be sent to the central lab to be reread and to qualify a sample for culture. The second slide should be retained at the investigator site.)

10. Revise the protocol to reflect that the central lab qualified Gram stain will be the one used to determine patient evaluability.
11. Define what organisms will be considered "valid pre-treatment pathogens" prior to study start.
12. Other than for *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, and *M. catarrhalis*, have the central lab provide semi-quantitative culture reports for all organisms the Sponsor wishes to consider pathogens.
13. Revise the definition of "clinical cure" to reflect that at minimum sputum volume, sputum purulence, dyspnea, and pulmonary function tests are improved from study entry to consider a patient improved enough to be considered a cure.
14. Revise the definition of "clinical failure" to "continuation or worsening of the signs and symptoms in ABECB at Evaluation 4 compared to Evaluation 1, or at the time of premature discontinuation from the study OR further additional antibiotic therapy is warranted."
15. Revise statistical plan to reflect the lower bound of delta to establish non-inferiority is -0.10 regardless of clinical cure rate.
16. Specify that the primary efficacy parameter (clinical cure rate) is at the Test-of-Cure visit. (The Agency views the clinical cure rate at the TOC visit in the evaluable and ITT populations as co-primary.)
17. Clearly state all planned secondary efficacy endpoints prior to study start

Tonsillopharyngitis M00-223  
 Dr. Dikoe Makhene

#### Comments Study Protocol

##### 1. General

- The Points to Consider document under the section entitled, ISSUES ABOUT SPECIFIC INFECTIONS, notes that applications for treatment of infections with dosing regimen durations less than generally approved

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for that infection should ordinarily contain two statistically adequate and well-controlled trials.

2. *Inclusion and Exclusion criteria*

- The December 1994 Pediatric Rule defines the pediatric population as patients up to 16 years of age. Therefore, the lower limit of age for enrollment should be raised from 12 years to 16 years of age. Since the sponsor is proposing a pediatric program, patients between the 12 and 15 years of age, with tonsillopharyngitis, can be studied during this part of the drug development.
- The FDA draft guidance document for this indication suggests that for inclusion in the study, at a minimum, patients should have a sore throat and at least one sign AND one symptom considered to be consistent with tonsillo-pharyngitis.
- Exclusion criterion 11, p. 15 discusses the exclusion of patients who have received a concomitant antimicrobial agent or systemic antimicrobial therapy in the 4 week (or 2 weeks as appropriate) prior to or during this study. It is unclear what the 4 weeks and 2 weeks refer to.
- Is the exclusion of patients who have received long acting penicillin within 4 weeks prior to study drug enough time before enrollment in the study?

3. *Definitions of Response*

*Clinical cure*

Definition of clinical cure should not include improved patients since after a full course of therapy all symptoms in patients with tonsillopharyngitis would be expected to be resolved.

*Clinical failure*

Clarify definition so that it does not give the impression that a patient is declared a failure only if they do not show improvement in clinical course AND a new antimicrobial agent is begun. If either condition is met, the patient is eligible to be considered a failure.

4. *Response rate*

A documented response rate of at least 85% will be necessary for an efficacy claim for this indication.

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5. Informed Consent

*Risks and Discomforts*

The protocol should include some discussion about the known cardiac adverse effects associated with this study drug. The consent should define why the EKG is needed so those patients can give informed consent before participation in this study.

*Reimbursement for Study Participation*

Please clarify the discrepant sentences, which state that "There is no monetary compensation available to you for your participation in this study" and "You will receive up to \_\_\_\_\_ for your participation in this study."

6. European Tonsillopharyngitis study

- Although the protocol has not been submitted for review, the sponsor has indicated those patients in this study will not have EKGs done beyond the baseline EKG.
- Because of the possibility of cardiac effects, patients in all the other studies with ABT-773, including the US tonsillopharyngitis study will have serial EKGs. Since there is nothing uniquely different about patients in the European tonsillopharyngitis study except location, and the potential risk to them is no less, patients in the European tonsillopharyngitis study should also have serial EKGs.

**Acute Bacterial Sinusitis M00-225**  
**Dr. Nasim Moledina**

1. In the Entry Criteria, the sinus X-ray or CT Scan should be done within 48 hours pre-treatment NOT 72 hours. This should also be corrected on the Case Report Form. The mucosal thickening on X-ray should be noted, using a criterion of more than or equal to 6mm as significant.
2. One of signs and symptoms to be included in the entry criteria is toothache.
3. As with ABECB, if patient is on theophylline for asthma, then those levels need to be monitored. The reason for doing this is that most (75%) of patients with sinusitis has allergies, and some of them may need to use theophylline.
4. More specific definitions to be given for CURE and Failure if the sponsor has included IMPROVED in the category of clinical success than that needs to be

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clarified in the protocol. The sinusitis protocol has different definitions for clinical outcome, and radiological outcome. The sponsor needs to be consistent.

5. The informed consent needs revision, as discussed at the meeting. The Division requests that a revised copy of the informed consent form to be submitted.

**Dr. Davidson - ABECB**

The protocol should also include the following:

1. Peak expiratory flow rate measurements should be obtained under the supervision of the investigator at each scheduled office visit, using instrumentation supplied by the sponsor; measurements should be recorded on the case report form.
2. Pulmonary function testing should be performed at Pre-therapy/entry visit, Post-therapy/TOC visit and late post-therapy visit.
3. Obtain baseline oximetry for oxygen saturation on room air or ideally, baseline arterial blood gas levels and at post-therapy/TOC visits. Blood gases or pulse oximetry and respiratory samples should be measured, in failures at late post-therapy visit.
4. The Divisions (DAIDP and DSPIDP) don't allow pooling PRSP isolates in CAP and AECB in order to support a PRSP claim in CAP.
5. At this time, we do not allow a PRSP claim in AECB.

**Issues Requiring Further Discussion: None**

Minutes Preparer: Jose R. Cintron, R.Ph., M.A.  
Senior Regulatory Management Officer

Chair Concurrence: Janice Soreth, M.D.  
Acting Division Director

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/s/

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Janice Soreth

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# Abbott Portfolio Review

March 7-9, 2001

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Project	ABT-518
Compound	Matrix Metalloproteinase Inhibitor
Presenter	Perry Nisen
Project Team Members	

A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

ABT-5188

- ◆ Target indication: Solid tumors
- ◆ Targeted unmet medical need: Cancer
- ◆ Target product profile vs. current gold standard:

[illegible]

## ABT-518

### ◆ Key pre-clinical findings:

#### – Pharmacology

- Potent and highly selective (gel-A and gel-B) MMP inhibitor
- Anti-tumor activity seen in numerous murine cancer models
- Inhibition of tumor growth is dose dependent
- Blocks vessel formation in a mouse model of angiogenesis

#### Pharmacokinetics / Metabolism in animals

- Sustained plasma concentrations following single-dose in monkeys
- Oral bioavailability between 68 and 93% in animals
- Multiple metabolites are produced after repeat dosing in rats and dogs

#### Toxicology

- No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
- No remarkable cardiovascular effects in dogs
- Steatosis seen in high-dose rats two weeks after drug stopped

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## ABT-518

### ◆Chemistry and Manufacturing

#### Drug substance

- Six steps from commercial starting materials
- 3-month turnaround time to manufacture
- Manufactured at Abbott

#### Drug product

- Neat drug in a capsule (25 and 200 mg) for Phase I
- Hand-fill or semi-automation at a third party manufacturing facility (Phase I)
- Formulation development work will begin post Phase II Go/No Go decision

## ABT-518

### ◆ Global clinical development plan

◆ Approval

◆ File NDA

Phase III

Phase II

Phase I

2006

2005

2004

2003

2002

2001

**ABT-518****◆ Clinical development budget**

Phase	Funding (\$MM)
Pre-Clinical	5
Phase I	12
Phase II	47
Phase III	78



## ABT-518

### ◆Phase I study:

#### Multiple-dose study in patients with advanced cancer

##### – Objectives

- Establish safety profile
- Determine the maximum tolerated dose (MTD)
- Assess PK
- Determine Phase II dose

##### Design

- 28 days + extension
- Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
- Approximately 40 patients; 3 patients per dose
  - Add 6 or more patients at MTD to collect additional safety information
- Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day



## ABT-518

### ◆ Phase I plan:

#### IND Study

##### – Objectives

- PD-guided Phase II dose selection
- Long-term safety

##### – Design

- Multiple dose escalation study
- Assess MMP activity in accessible tumors
  - Melanoma
  - Head and Neck Cancer
- Approximately 20 patients

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## ABT-518

### ◆Phase II development plans:

- 3 Studies
  - 3 Tumor types as defined by Phase I and animal efficacy
  - 150 patients per study
- Dose finding
- Assess safety issues identified in Phase I
- Thirteen month duration

## ABT-518

### ◆Phase III plan:

- Demonstrate improvement in survival or TTP in combination with cytotoxic therapies

## Strategic Summary

### ABT-518

#### ◆Key project strengths / positives:

##### – Product attributes

- Highly selective for the inhibition of gelatinases A & B
- Very potent
- No joint-toxicity expected
- Potentially best in class

##### – Technology / Innovation

- Oral, once-a-day dosing

##### – Time to market

- Potential for fast-track approval
- Launch 2Q06

##### – Business franchise strength

- Comprehensive oncology franchise
- Synergies with HPD and ADD

##### – Other relevant points

- Competitors in class
- Non-oncologic indications
  - » Multiple sclerosis
  - » Proliferative retinopathy
  - » Arthritis



***ABT-773 Portfolio Review***  
*December 5, 2000*

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ABBT205086

## *Agenda*

*Part 1: General Overview, Tablet*

- 
- **Introduction-Carl Craft (5 min)**
  - **Executive Summary-George Aynilian (10 min)**
  - **Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)**
  - **Microbiology-Bob Flamm (20 min)**
  - **Tablet Clinical Program**
    - Phase II data-Joaquin Valdes (20 min)
    - Phase III clinical plan-Joaquin Valdes (10 min)
  - **SPD Summary-Ashok Bhatia (10 min)**
  - **Tablet Key Issues**
    - Analysis of QT/Liver data-Dave Morris (20 min)
    - PK profile-Linda Gustavson (10 min)
    - Regulatory-Jeanne Fox (10 min)
    - Timeline risk George Aynilian (5 min)
  - **Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)**



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## Agenda

Part 2: I.V., Pediatric, Japan, Q&A

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- I.V. Program/Issues-Carol Meyer (5 min)
- Pediatric Program/Issues-Carol Meyer (5 min)
- Japan Program/Issues-Carol Meyer (5 min)
- ABT-492 (time permitting)
  - timeline
  - budget
  - rationale
- Summary-Carl Craft (5 min)
- Q&A



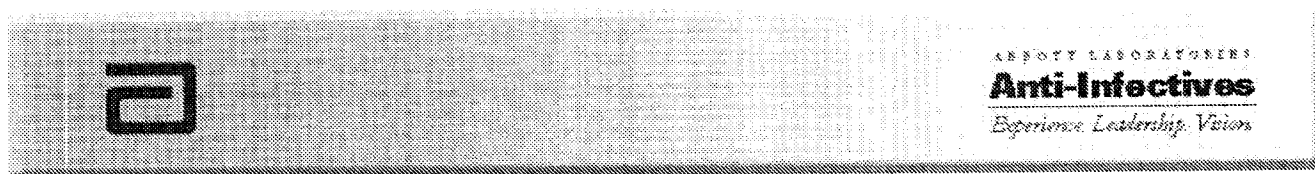
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**ABT-773**  
*Executive Summary*

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- **Management**
  - Established European Clinical Team (11 dedicated members)
  - Plans ongoing to strengthen Japan team
  - Completed staffing of Abbott Park team
  - Established communication team
  - Completed conceptual model of study tracking application (web based)
  - Established integrated project management system



## **ABT-773**

### *Executive Summary*

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- **Chemistry**
  - Exceeded '00 goals for yield, cost/Kg and deliveries
  - Task Force implemented modification of 3 steps
  - 3 TPMs for intermediates well established
  - Prepared package for justifying Step 5 as starting material



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## **ABT-773**

### *Executive Summary*

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- **Tablet Formulation**
  - Scale up operations at AP and IDC on target
  - Linkage of materials between scales and sites being established by bioequivalency trials.
  - NDA runs and stability were initiated for 08/02 filing.



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**ABT-773**  
*Executive Summary*

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- **IV Formulation**

- Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.

- **Pediatric formulation**

- Phase I complete with two prototypes. After- taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget

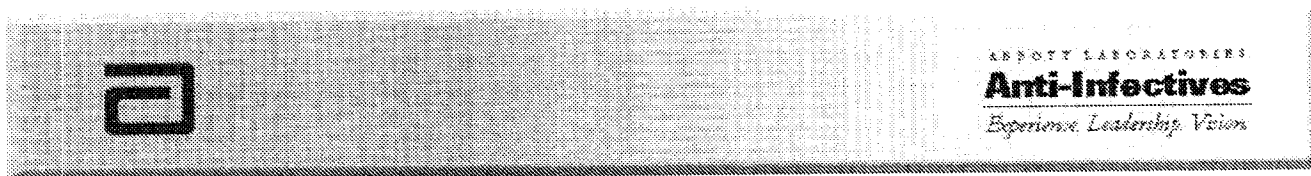


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**ABT-773**  
*Executive Summary*

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- **Preclinical Safety**
  - Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPII meeting with FDA.
- **Molecular Biology**
  - Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.



**ABT-773****Executive Summary**

- 
- **Clinicals**
    - Completed Three Phase IIb studies
    - Decision Support Analysis completed
    - Dose selection 150mg and 150mg bid
    - Initiated Phase III program( 6 studies, 4 under IND)
    - Completed all Investigator's meetings
    - Regulatory meetings
      - UK, Germany, France, US
  - **End of Phase II package**
    - Document sent to FDA X/X
    - End of phase II meeting held with FDA 11/26
  - **Japan bridging study/Kiko Mtg/Repeat Phase I in Japan**



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**ABT-773**  
*Executive Summary*

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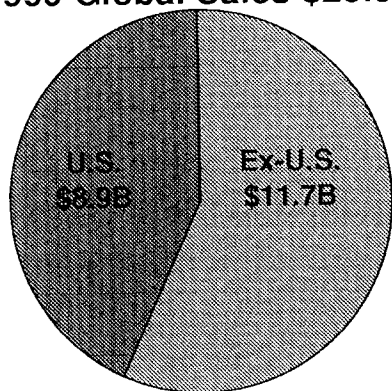
- **Key Events (Nov '00-June '01)**
  - Initiate Phase III (ABECB, ASP, ABS, CAP) in US/EU
  - End of Phase II meeting with FDA (New amendment, informed consent)
  - Initiate Japan Phase I program in Japan
  - Results of Phase III (CAP/ABS) studies
  - Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
  - Set up balance of Phase III studies (CAP/ABS) 4 studies



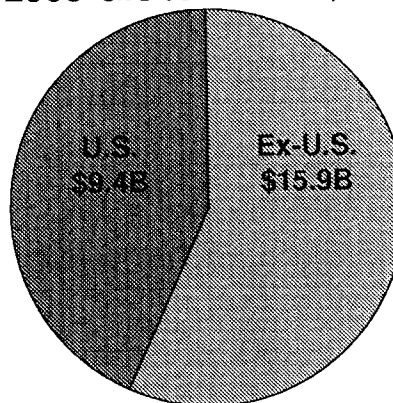
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**Global Antibiotic Market Sales**  
*Current vs Future Projection*

**1999 Global Sales \$20.6B**



**2005 Global Sales \$25.3B**



The antibiotic market is a large market and is expected to expand on a global sales basis

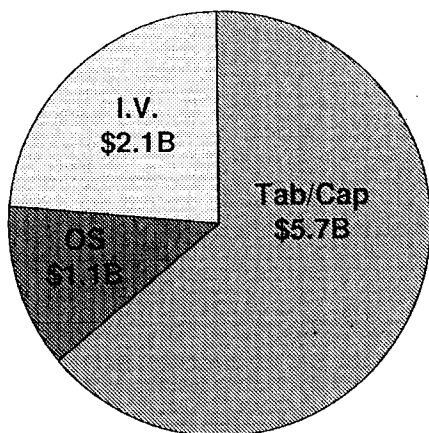


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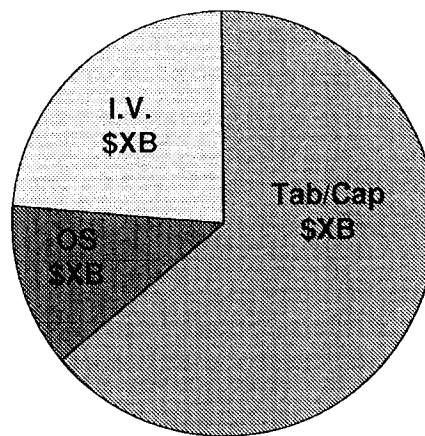


**Global Antibiotic Market Sales**  
by Formulation

1999 U.S. Sales \$8.9B



1999 Ex-U.S. Sales \$11.7B



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## Key Competitors

### U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactams	Other	Injectables*
Abbott	\$956	\$740		\$48	\$3	\$165
Pfizer	\$1,366	\$1,076	\$71	\$3	\$3	\$213
SB	\$1,303			\$1,229		\$74
Bayer	\$1,034		\$911		\$1	\$122
J&J	\$797		\$612			\$185
Roche	\$526				\$10	\$516
Glaxo	\$551		\$6	\$425	\$28	\$92
BMS	\$387		\$1	\$386		
Lilly	\$107			\$33		\$74
Others	\$1,670	\$95	\$27	\$631	\$298	\$619
'99 Total	\$8,790	\$1,911	\$1,628	\$2,755	\$343	\$2,153
'98 Total	\$7,570	\$1,592	\$1,331	\$2,453	\$272	\$1,922
% Chg	16.12%	20.04%	22.31%	12.31%	26.10%	12.02%
TY vs LY						
* Includes IV form of all classes						
Source: IMS						

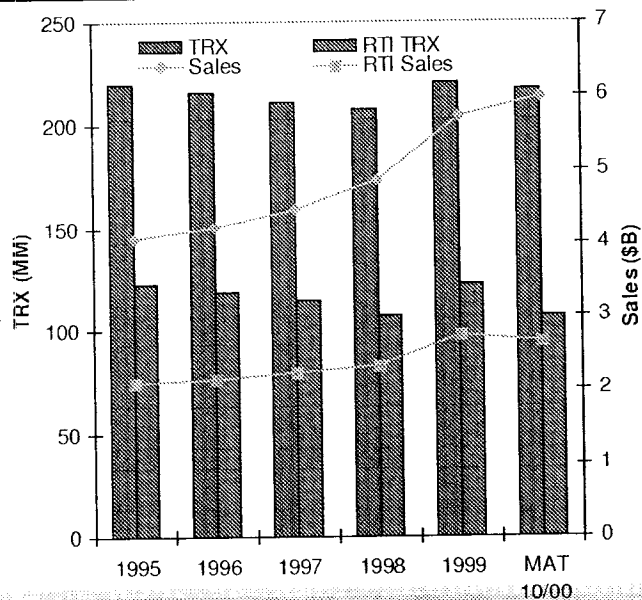
### Ex-U.S. Market

	Franchise	Macrolides	Quinolones	Beta-Lactam	Injectables	Other
Abbott	\$ 717	\$679	\$ 22	\$ 3	\$ 13	\$0
Shionoi Seiyaku	\$ 969	\$ 2	\$ 3	\$ 432	\$ 466	\$ 66
Pfizer	\$ 664	\$267	\$ 12	\$ 68	\$ 245	\$ 71
SKB	\$ 842	\$ 0	\$ 0	\$ 780	\$ 61	\$ 0
BMS	\$ 547	\$ 0	\$ 2	\$ 378	\$ 154	\$ 13
Roche	\$ 460	\$ 0	\$ 3	\$ 43	\$ 303	\$112
Bayer	\$ 524	\$ 0	\$437	\$ 43	\$ 43	\$ 1
Lilly	\$ 437	\$ 28	\$ 0	\$ 337	\$ 66	\$ 6
Fujisawa Yakuhin	\$ 522	\$ 0	\$ 0	\$ 411	\$ 111	\$ 0
Daiichi Seiyaku	\$ 497	\$ 0	\$497	\$ 0	\$ 0	\$ 0
'99 Sub-total	\$6,178	\$977	\$976	\$2,495	\$1,461	\$269



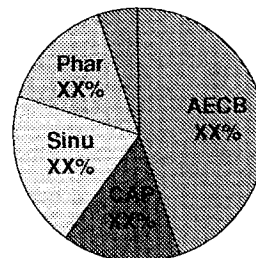
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### U.S. Tab/Cap Antibiotic Market TRX & Sales Trends



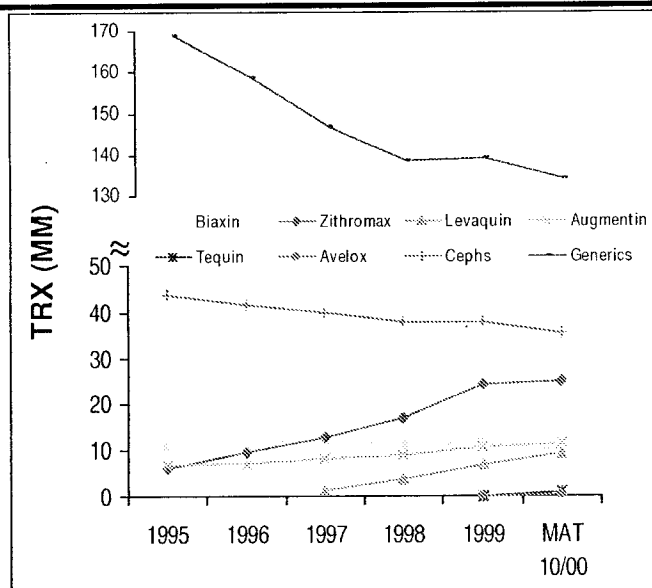
- While negative pressure exists on antibiotic usage, market sales have increased substantially
- TRX CAGR<sub>95-99</sub> = + 0.1%
- Sales CAGR<sub>95-99</sub> = + 8.9%

#### RTI Sales by Indication

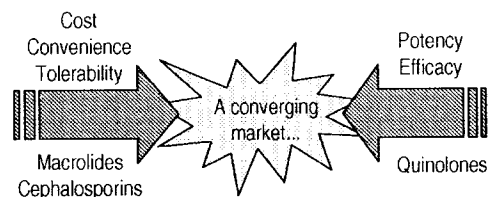


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### U.S. Tab/Cap Antibiotic Market Product Trends

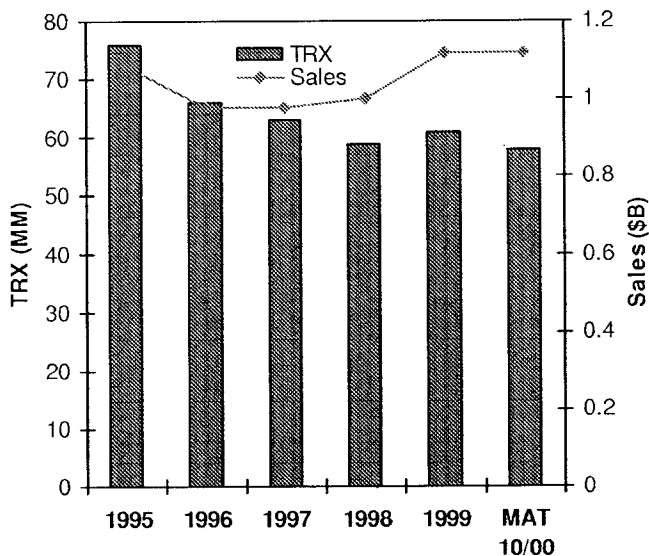


- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Zithromax has driven market demand for cost/convenience/tolerability
- Quinolones (Levaquin, Tequin, Avelox) are fastest growing segment, playing into resistance concerns; 1998-99 growth of 15% (TRX) & 22% (\$)



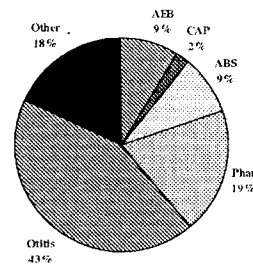
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### U.S. Pediatric Antibiotic Market TRX & Sales Trends



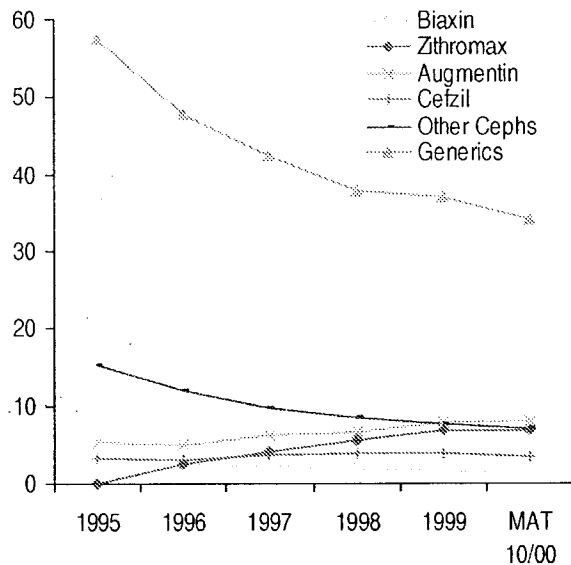
- TRX CAGR<sub>95-99</sub> = - 5.4%
- Sales CAGR<sub>95-99</sub> = + 1.0%
- TRX under greater pressure than Tab/Cap market
- Recent leveling in sales

Sales by Indication



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### ***U.S. Pediatric Antibiotic Market*** *Product Trends*

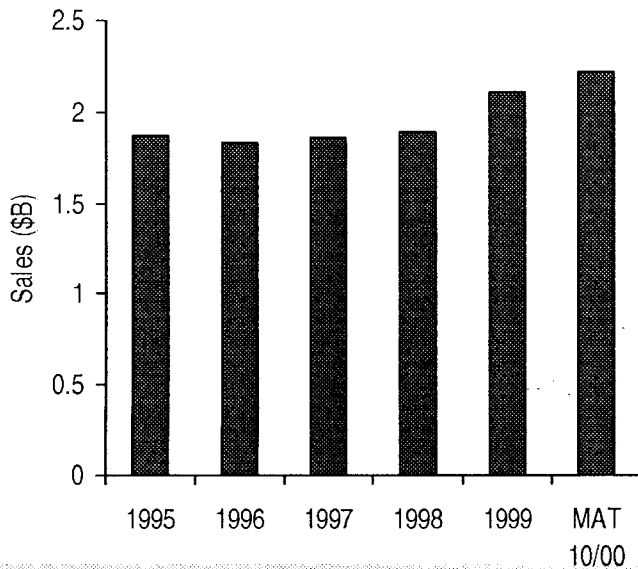


- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand



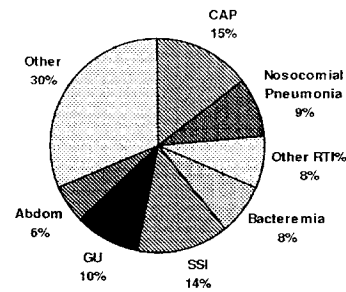
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## U.S. Injectable Antibiotic Market Sales Trends



- Current Market: \$2.1B, CAGR = + 3.2%
- Two market segments:
  - Severe community-acquired
    - Rocephin, Levaquin, Tequin, Zithromax
  - Nosocomial
    - Synercid, Zyvox, vancomycin

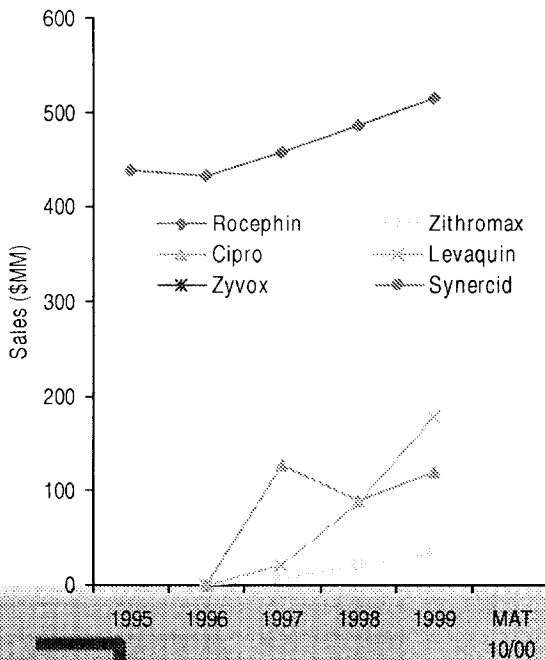
Uses by Indication



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### U.S. Injectable Antibiotic Market Product Trends



- Rocephin is market leader, quinolones as class are making good gains
- Availability of I.V. has spill-over effect on tablet business
  - direct sales from step-down
  - enhances image of potency
  - more compelling package to managed care



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## **Global Market Drivers**

### ***Negative vs Positive Drivers***

- Antibiotic Resistance

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓

Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

- Patent Expirations

May increase price sensitivity and bargaining power of MCOs ↓

Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

- Market expansion ex-US ↑

- Unmet Need ↓

- Overall unmet need relatively low

- Cost, convenience, tolerability take on added importance

- Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

- Competition ↓

- 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox

- Continued discovery/development activity by key competitors

- High level of promotional activity

Negative driver ↓

Positive driver ↑

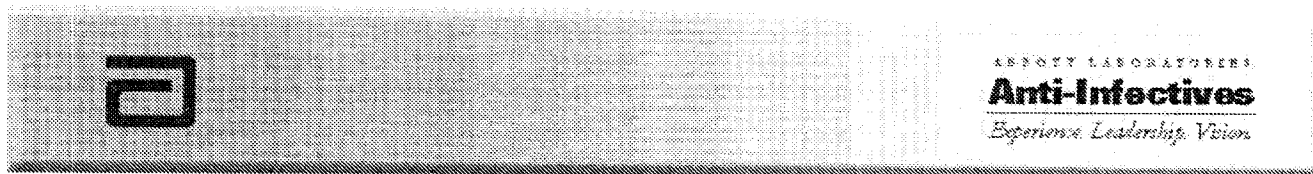


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- 
- Resistance surveillance



Confidential

ABBT205108

***Patent Expirations***  
*Expiration & At Risk Sales*

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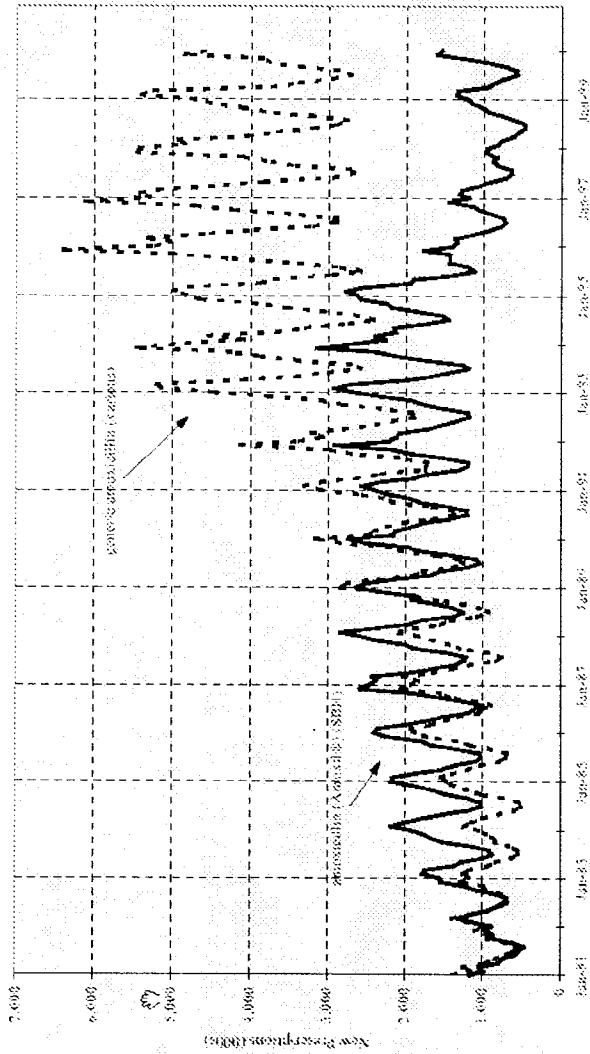
	<u>Year</u>	<u>1999 U.S. Sales</u> <u>(\$MM)</u>
Ceftin	2003	\$425
Cipro	2003	\$1,023
Biaxin	2005	\$756
Cefzil	2005	\$357
Levaquin	2005	\$708
Zithromax	2005	\$1,111

\$5,540



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Figure 139. SBH's Amoxil® vs. generic amoxicillin, 1981-2000 (New Prescriptions, monthly data)

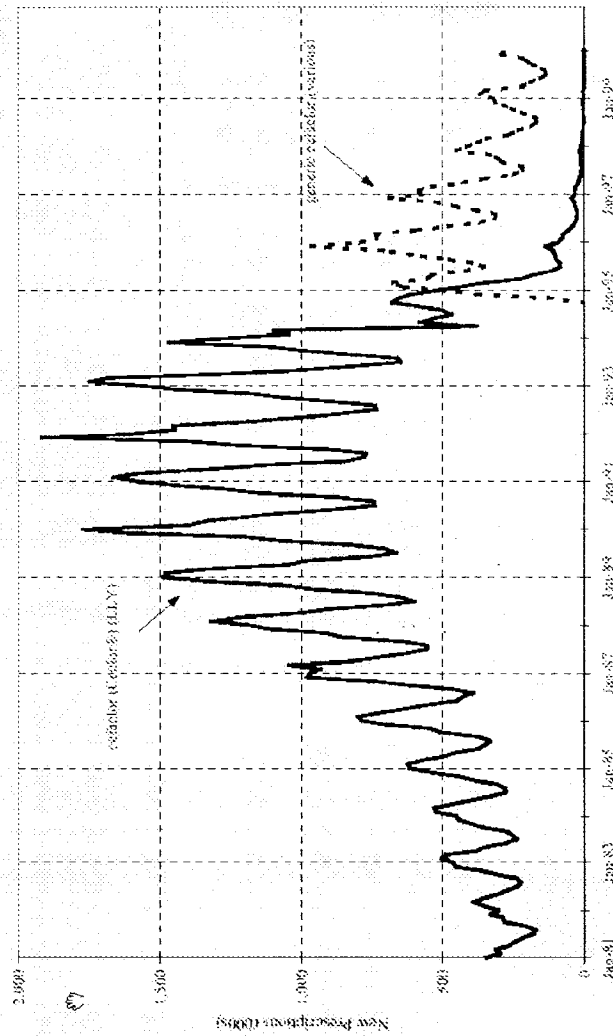


Source: IMS, U.S. prescription market, Retail only

ABBT 205110  
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Figure 140. Lilly's Cefactor® vs. generic cefactor, 1981-2000 (New Prescriptions, monthly data)



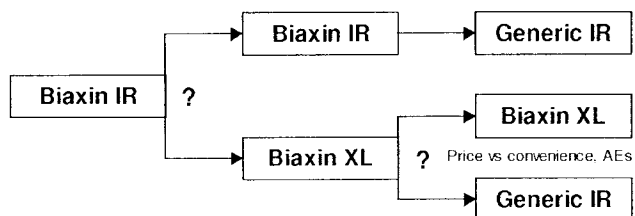
Source: IMS, U.S. prescription market. Retail only.

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## Biaxin Patent Expiration

### Biaxin/773 Scenarios



		XL==> Generic Conversion		
		Low	Med	High
IR ==> XL Conversion	Low	?	C	C
	Med		?	C
	High			?

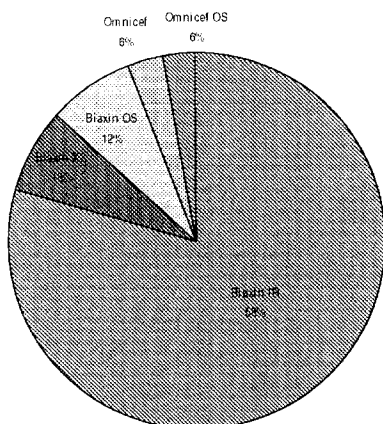
C = Convert Biaxin to ABT-773  
Assumes high conversion rate of IR to generics



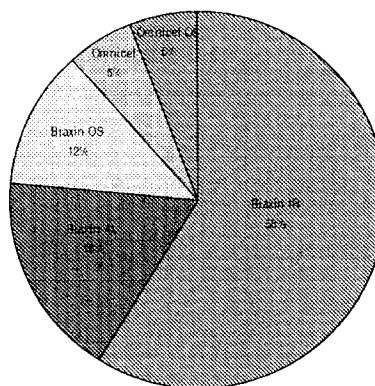
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## Abbott Anti-Infective Franchise 2001 Plan

U.S. Sales = \$794 MM



Ex-U.S. Sales = \$XXX MM



The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005



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**ABT-773 Profile**

	Current Profile
Dosing	150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD)
Efficacy	ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication
Adverse Events (150 mg QD)	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%
Resistance Claim	Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V.



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**ABT-773 Profile**  
vs Biaxin XL

	ABT-773	Biaxin XL
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1%
Resistance Claim	Being pursued	Under exploration



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# PART 2

## ***Key Commercial Challenges***

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- **150 mg QD vs 150 mg BID**
  - 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
  - Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies==> QD and BID development programs, increased cost
- **PK**
  - Negative implications for efficacy as well as resistance development
- **H. flu eradication**
  - dose-defining pathogen, limited number of data points to date
  - a strength of quinolones
- **Tolerability may be sub-optimal**
  - diarrhea and taste perversion
- **2nd to market ketolide**
  - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29



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**Phase II Data: 150 mg QD vs 300 mg QD**

			Phase IIb Data: Intent-to-treat							
			Bronchitis		CAP		Sinusitis		Total	
Clinical Cure	150 mg QD		85%	104/123	-	-	82%	72/88	83%	176/211
	300 mg QD		83%	107/129	84%	80/95	80%	72/90	82%	159/314
Bacteriological Cure	<i>H. flu</i>	150 mg QD	89%	17/19	-	-	60%	3/5	83%	20/24
		300 mg QD	81%	17/21	100%	9/9	100%	7/7	89%	33/37
	<i>S. pneumo</i>	150 mg QD	77%	10/13	-	-	100%	3/3	81%	13/16
		300 mg QD	90%	9/10	82%	14/17	100%	8/8	89%	31/35



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## ***Ketek Summary***

### ***Regulatory Status***

---

- **Ketek (telithromycin, Aventis) will be first-to-market ketolide**
- **U.S.**
  - Filed with FDA March 2000
  - **FDA advisory 1/29**
  - Expected approval 1Q01
- **Ex-U.S.**
  - Package submitted to EMEA as centralized filing in March 2000
    - Rapporteur = Sweden
    - Co-rapporteur = Portugal
    - Expected approval 1Q01
- **Phase II in Japan (source: IMS World R&D Focus)**



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## **Ketek Summary**

### **Profile Summary**

- 800 mg QD for all indications
- AECB (5 d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
- High rate of diarrhea (10-20%), nausea (10%), but no taste perversion
  - statistically greater diarrhea vs trovafloxacin in phase III study
- Comparable levels of efficacy to comparators (see appendix for full clinical summary)
  - 74%-95% clinical cure
  - 69%-94% overall eradication
  - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication; an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
- Liver function elevation
  - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
- QTc prolongation: Aventis maintains no clinically relevant impact
- High COGS based on SPD pricing on intermediate
  - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for 773 at launch
  - may limit pricing flexibility
- Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
  - eradication rate with these isolates unknown, important factor in FDA decision



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**Ketek Summary**  
**ABT-773 Comparison**

	ABT-773	Ketek
Dosing	ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d	All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?)
Efficacy	ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data	ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad
Adverse Events	Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2%	Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ???
Resistance Claim	Being pursued	Submitted in NDA



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## **Ketek Summary**

### **ABT-773 Strengths/Weaknesses**

---

#### ABT-773 Strengths vs Ketek

- ABT-773 is considerably more potent than telithromycin against:
  - resistant and susceptible strains of *S. pneumo*
  - atypicals
  - H. flu (based on in vivo animal models)
- Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- Mechanistic advantages
  - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- Potential for greater pricing flexibility

#### ABT-773 Threats/Issues vs Ketek

- 2nd to market
- Potential for BID dosing in CAP and/or sinusitis
- ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- PK profile



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## Ketek Summary

### Clinical Data

Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>Pharyngitis #1</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>CAP #1</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>CAP #2</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>CAP #3</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>CAP #4</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>Strains #1</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>Strains #2</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>Strains #3</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%
<b>Strains #4</b>	Ketek 800 mg, 2 x 5 d	Amoxicillin 500 mg, 2 x 10 d
Cure	95%	97%
Eradication	97%	94%
Duration	79%	81%
Values	79%	81%
Side effects	6%	4%

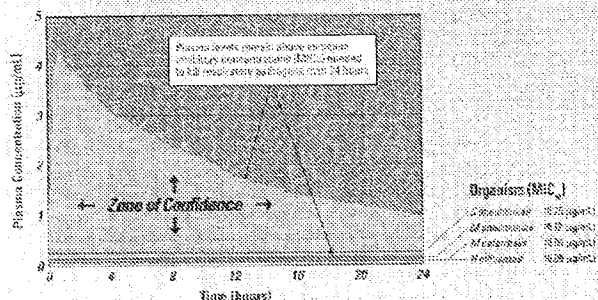


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## PK Issue

**AVELOX provides a 24-hour *Zone of Confidence* covering key respiratory pathogens<sup>1</sup>**

**Steady-state plasma concentrations are well above MIC<sub>90</sub>s of key community respiratory pathogens<sup>1</sup>**

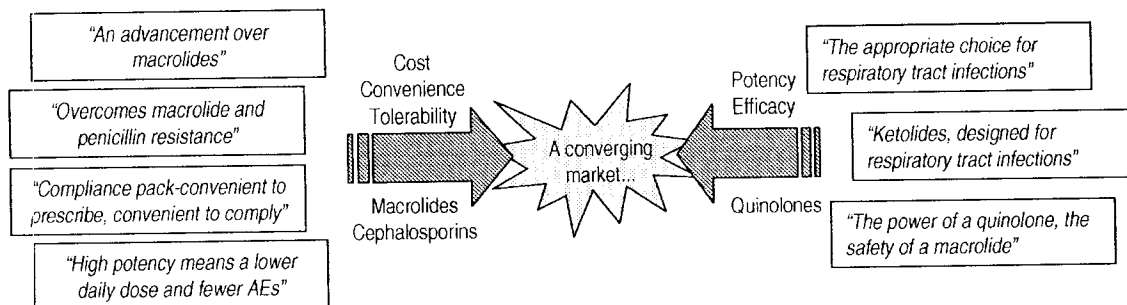


Quinolones are using PK as means of differentiating products-could increase the relevance of PK to prescribers

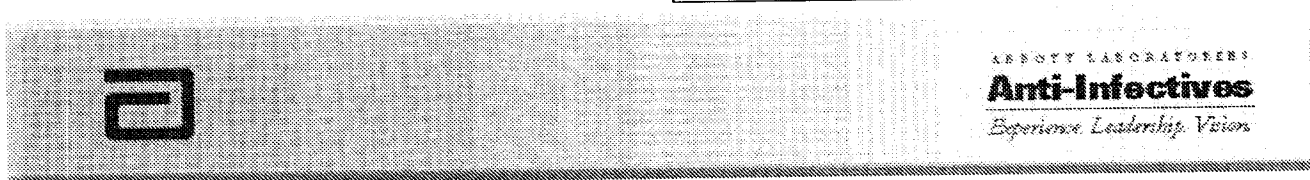
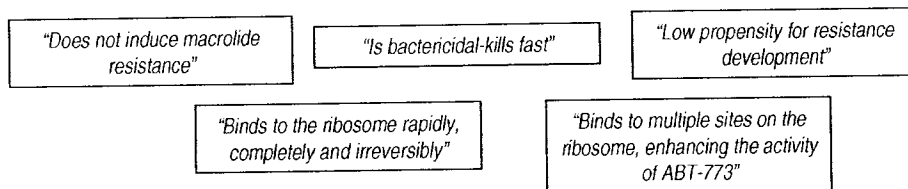


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## Key Commercial Messages



### Supportive Messages



## ***Communications Strategy***

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- Messages
  - microbiological data (resistance, the better ketolide)
  - PK (no food effect, favorable drug-drug)
  - Mechanism (ribosome binding, PAE, etc., “explanation” for ketolide activity, defense of dose selection)
  - Clinical data
- Implementation
  - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
  - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
  - Publications (10 publications in 2000)
  - Medical Liaisons(sp)
  - VIP Visits



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## ICAAC 2000

*International Conference on Antimicrobial Agents and Chemotherapy, Toronto*



See you at ICAAC 2001, in  
Chicago, Illinois!!

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**Forecast Assumptions**

	<u>US</u>	<u>Europe</u>	<u>Japan</u>
Dosing	150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d		
Efficacy	Comparable to other agents		
AEs	Comparable to Biaxin XL		
COGS	\$3,000/kg at launch		
AWP/Day	\$8.60		



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**Forecast**


---

	<u>U.S.</u>	<u>Europe</u>	<u>Japan</u>	<u>ROW</u>	<u>Total</u>
Peak Sales	\$432MM				
Peak TRX Share	7.5%				N/A
NPV @12.5%					



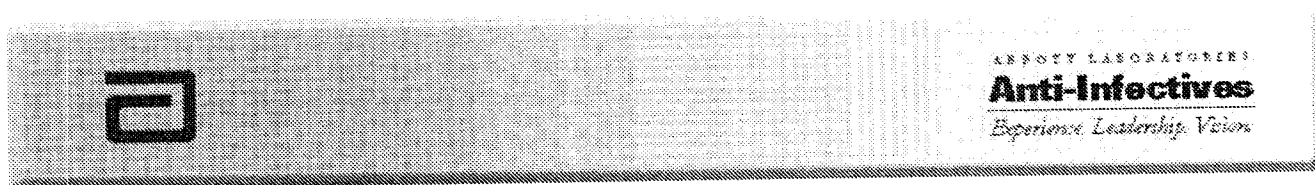
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## **Microbiology**

### *Overview*

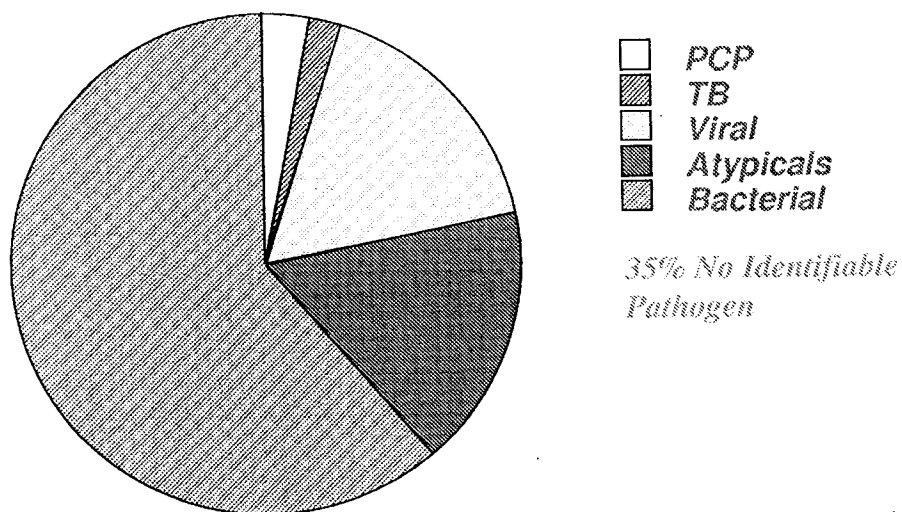
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- **Ketolides are a Novel Class of Antimicrobial**
  - Active vs. key respiratory tract infection pathogens to include macrolide resistant streptococci
  - Bactericidal activity
  - Prolonged post antibiotic effect
  - Reduced resistance development

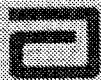




**Microbiology**  
*Community-Acquired Pneumonia in Adults*



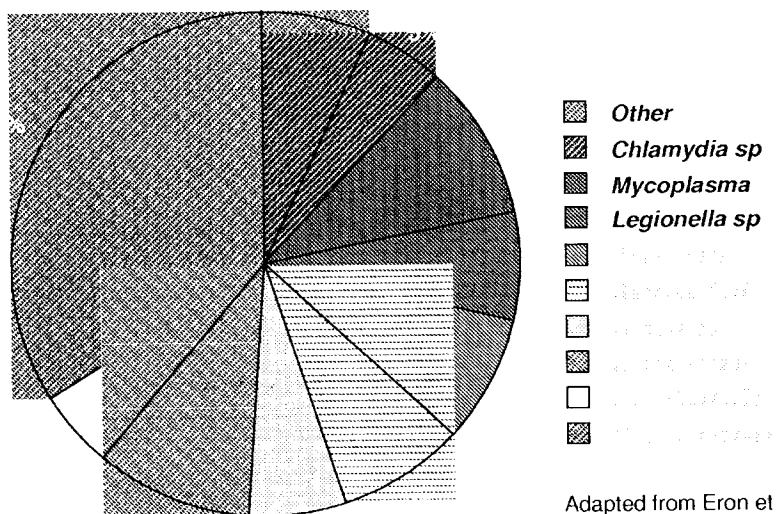
Adapted from Eron et al. Hosp Form 1994;29:122



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## Microbiology

### *Bacterial Causes of Community-Acquired Pneumonia in Adults*



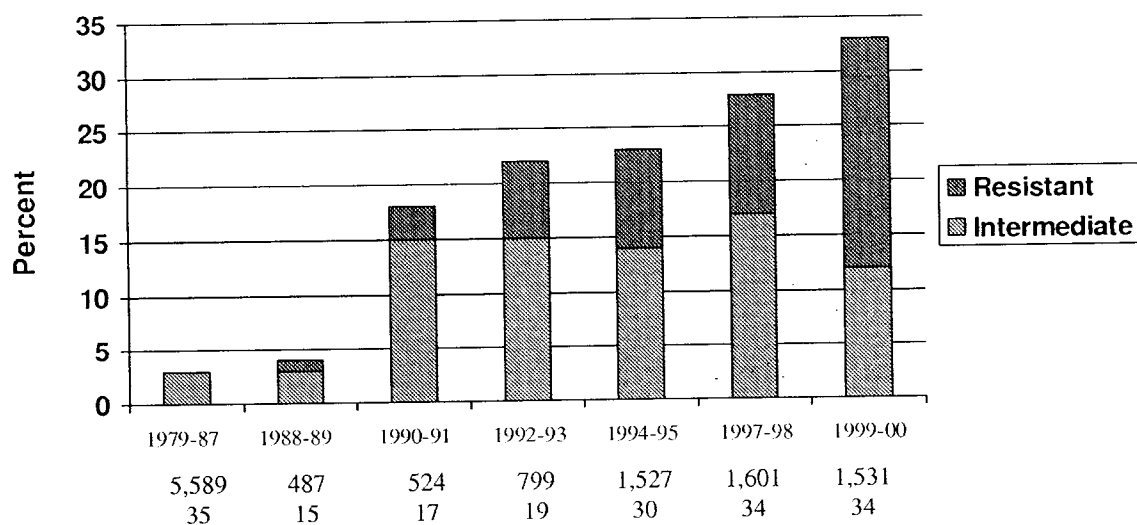
Adapted from Eron et al. Hosp Form 1994;29:122



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**Microbiology**

***Penicillin resistance with *Streptococcus pneumoniae* in the United States***



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**Microbiology****US Respiratory Surveillance Studies, Penicillin Susceptibility in *S. pneumoniae***


---

Year	1994-95	1997-98	1999/2000
Season	Winter	Winter	Winter
No. of centers	30	34	34
No. of isolates	1,528	1,601	1531
No. % intermediate	216 (14.1)	278 (17.4)	194(12.7%)
No. % resistant	145 (9.6)	196 (12.2)	29 (21.5%)

Dr. G. Doern, Univ. of Iowa



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**Microbiology**  
**Antimicrobial Resistance Rates among *S. pneumoniae***

	1994-95	1997-98	1999-2000
Antimicrobial Agent	N=1527	N=1601	N=1531
Macrolide	10.0	18.9	25.9
Tetracycline	7.5	12.9	16.4
Chloramphenicol	4.3	7.2	8.4
Clindamycin	Na	5.6	8.8
TMP/SMX	18.0	20.4	30.3

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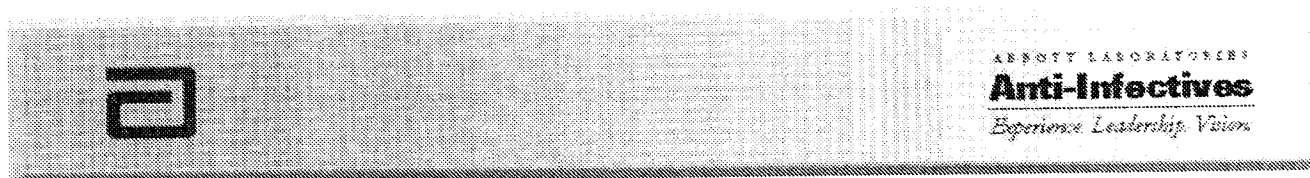
**Microbiology**

*Rates of Resistance of Non-  $\beta$  -Lactam Antimicrobials with Streptococcus pneumoniae  
Based on Penicillin Susceptibility Category*

Percentage Resistance Among

Antimicrobial	PenS-(n=1,008)	PenI(n=194)	PenR(n=1,531)
Macrolides	5.6	43.3	78.1
Clindamycin	1.4	19.1	25.2
Chloramphenicol	1.0	13.9	27.7
Tetracycline	3.1	32.0	48.0
TMP/SMX	7.6	39.2	94.5

[n=1,531, 34 U.S. centers, 1999-2000], Doern et al



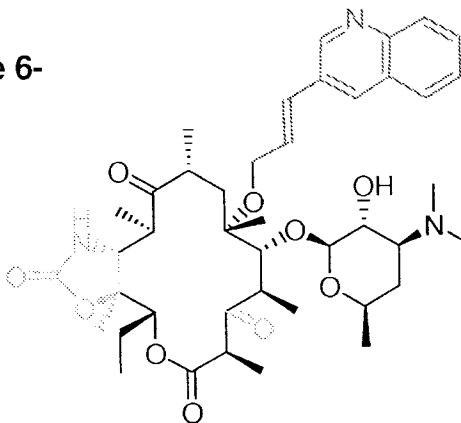
**Microbiology**  
**ABT-773 Structure/SAR**

---

•Quinolylallyl propenyl moiety at the 6-  
O -position

•Keto group at the 3-position

•Carbamate group at the  
11, 12-position



**ABT-773**

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**Microbiology**  
*Macrolide Resistance Types*

---

**Microbiology Overview**

• **Two major macrolide resistance mechanisms in streptococci and staphylococci:**

- Ribosomal methylase – blocks macrolide binding to target
  - Macrolide and clindamycin MIC >16 µg/mL
- Macrolide efflux – actively pumps macrolide out of cell
  - Macrolide MIC 1-32 µg/mL; clindamycin MIC ≤ 0.25 µg/mL



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**Microbiology**

**Resistance Mechanisms Prevalence in *S. pneumoniae* Clinical Isolates**

---

Genotype	U.S. 1994-95 <sup>1</sup> n=114	U.S. 1997-98 <sup>2</sup> n=302	Canada <sup>3</sup> n=147	Europe <sup>4</sup> n=21	Japan <sup>5</sup> n=62
<b><i>ermB</i></b>	<b>32%</b>	<b>29%</b>	<b>39%</b>	<b>97%</b>	<b>40%</b>
<b><i>mefE</i></b>	<b>61%</b>	<b>71%</b>	<b>56%</b>	<b>3%</b>	<b>43%</b>
<b><i>mef/erm</i></b>	<b>5%</b>	<b>-</b>	<b>&lt;1%</b>	<b>-</b>	<b>16%</b>
<b>Unknown</b>	<b>2%</b>	<b>-</b>	<b>6%</b>	<b>-</b>	<b>0%</b>

<sup>1</sup>Shortridge, et al. *CID*. 1999; 29:1186-8.

<sup>2</sup>Doern, et al. *EID*. 1999; 5(6).

<sup>3</sup>Johnston, et al. *AAC*. 1998; 42:2425-26.

<sup>4</sup>Schmitz et. al. *JAC*. 1999.43:783-92

<sup>5</sup>Nishijima et. al. *JAC*. 1999.43:637-643



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**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Erythromycin MIC**

Drug	Erythromycin MIC $\leq 0.5 \mu\text{g/ml}$ (n=1299)		Erythromycin MIC 1-32 $\mu\text{g/ml}$ (n=222)		Erythromycin MIC $\geq 64 \mu\text{g/ml}$ (n=80)	
	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.12$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.5$

1997-1998 Survey, Brueggemann et. al.2000. AAC. 44:447-449



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# PART 3

**Microbiology****ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Penicillin MIC**

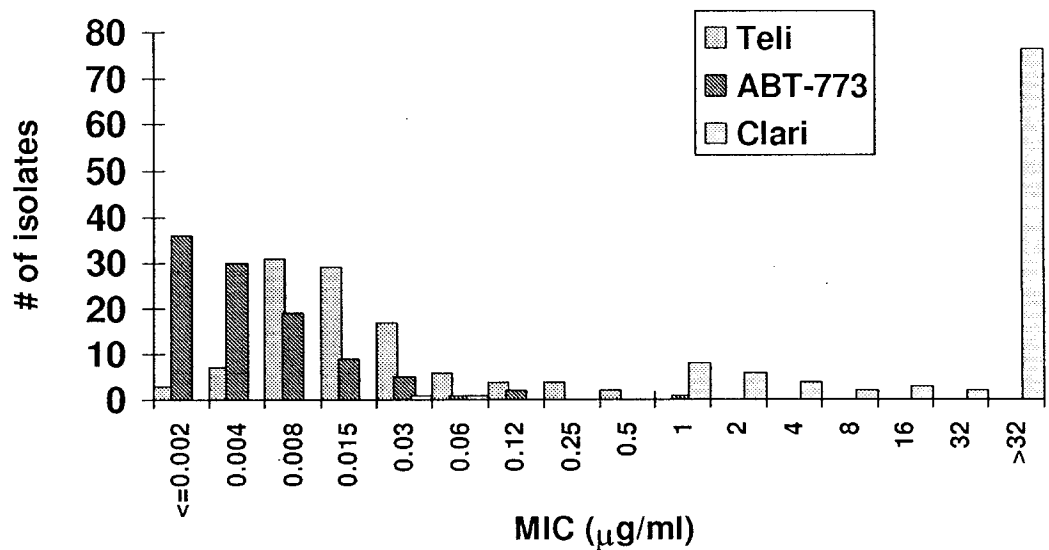
	Penicillin Susceptible MIC $\leq 0.06$ $\mu\text{g/ml}$ (n=1127)		Penicillin Intermediate MIC 0.12-1.0 $\mu\text{g/ml}$ (n=278)		Penicillin Resistant MIC $\geq 2.0$ $\mu\text{g/ml}$ (n=196)	
Drug	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range	MIC <sub>90</sub>	MIC range
ABT-773	$\leq 0.008$	$\leq 0.008 - 0.5$	0.03	$\leq 0.008 - 0.5$	0.12	$\leq 0.008 - 0.25$
Ery	0.06	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$	>64	$\leq 0.03 - >64$

1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449



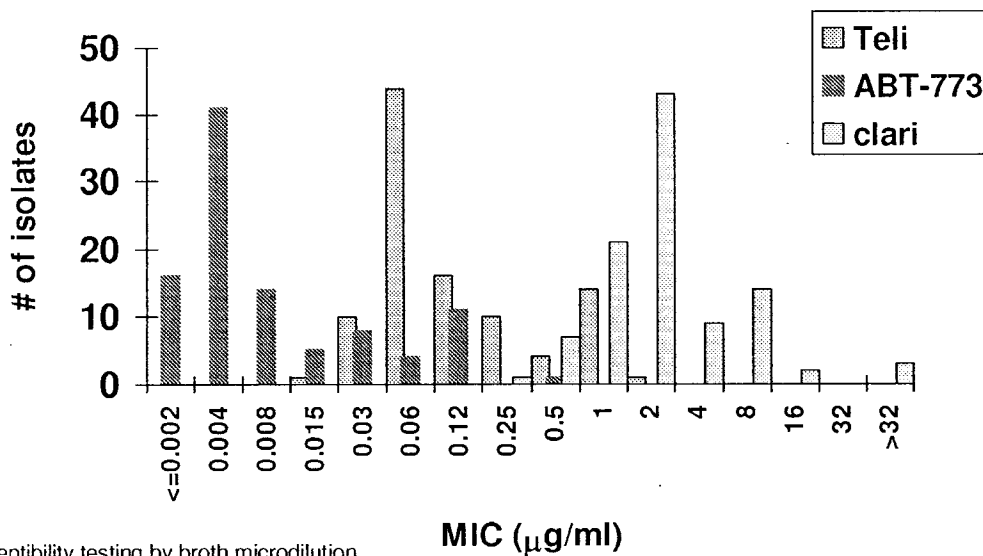
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**Microbiology**  
*MIC Distribution of S. pneumoniae methylase<sup>+</sup> strains*

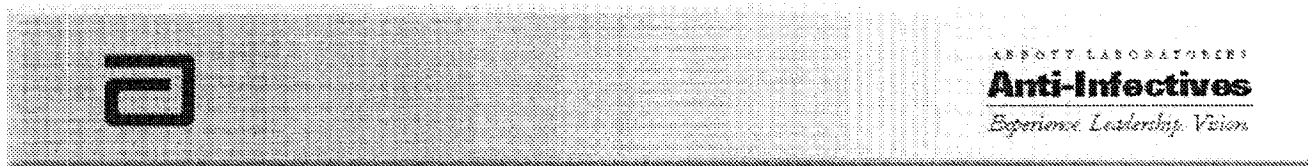


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**Microbiology**  
*MIC Distribution of S. pneumoniae efflux<sup>+</sup> strains*



Susceptibility testing by broth microdilution



**Microbiology**  
*In vitro Activity, S. pyogenes*

MIC<sub>90</sub> Range in µg/ml

Organism	Macrolide susceptible	Macrolide resistant
ABT-773	≤0.016 - 0.03	0.06 - 0.12
Erythromycin	0.06 - 0.12	8 - 16

References:

Barry et al ICAAC 1999 #2144

Dubois et al. ICMASKO 2000 #2.15

Singh et al. ICMASKO 2000 #2.14



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**Microbiology***In vitro Activity , Haemophilus, Moraxella spp.***MIC<sub>90</sub> Range in µg/ml**

Organism	<i>H. influenzae</i>	<i>M. catarrhalis</i>
ABT-773	2 - 4	0.06 – 0.25
Azithromycin	2 - 4	0.06 - 0.12
Erythromycin	8 - 16	0.25 - 0.5

## References:

Barry et al ICAAC 1999 #2144

Hoellman et al ICAAC 1999 #2140

Brueggemann et al. 2000.AAC.44:447-449

Shortridge et. al.1999. ICAAC



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**Microbiology****Comparison of activity vs. respiratory atypical pathogens**MIC<sub>90</sub> in µg/ml

Organism	ABT-773	Ery
<i>Legionella</i> spp. <sup>1</sup> (105)	0.03-0.12	0.25-1.0
<i>M. pneumoniae</i> <sup>2</sup> (18)	≤ 0.0005	0.008
<i>C. pneumoniae</i> <sup>3</sup> (20)	0.015	0.06

<sup>1</sup>Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10).

<sup>2</sup>Nilius et al. ECCMID 1999.

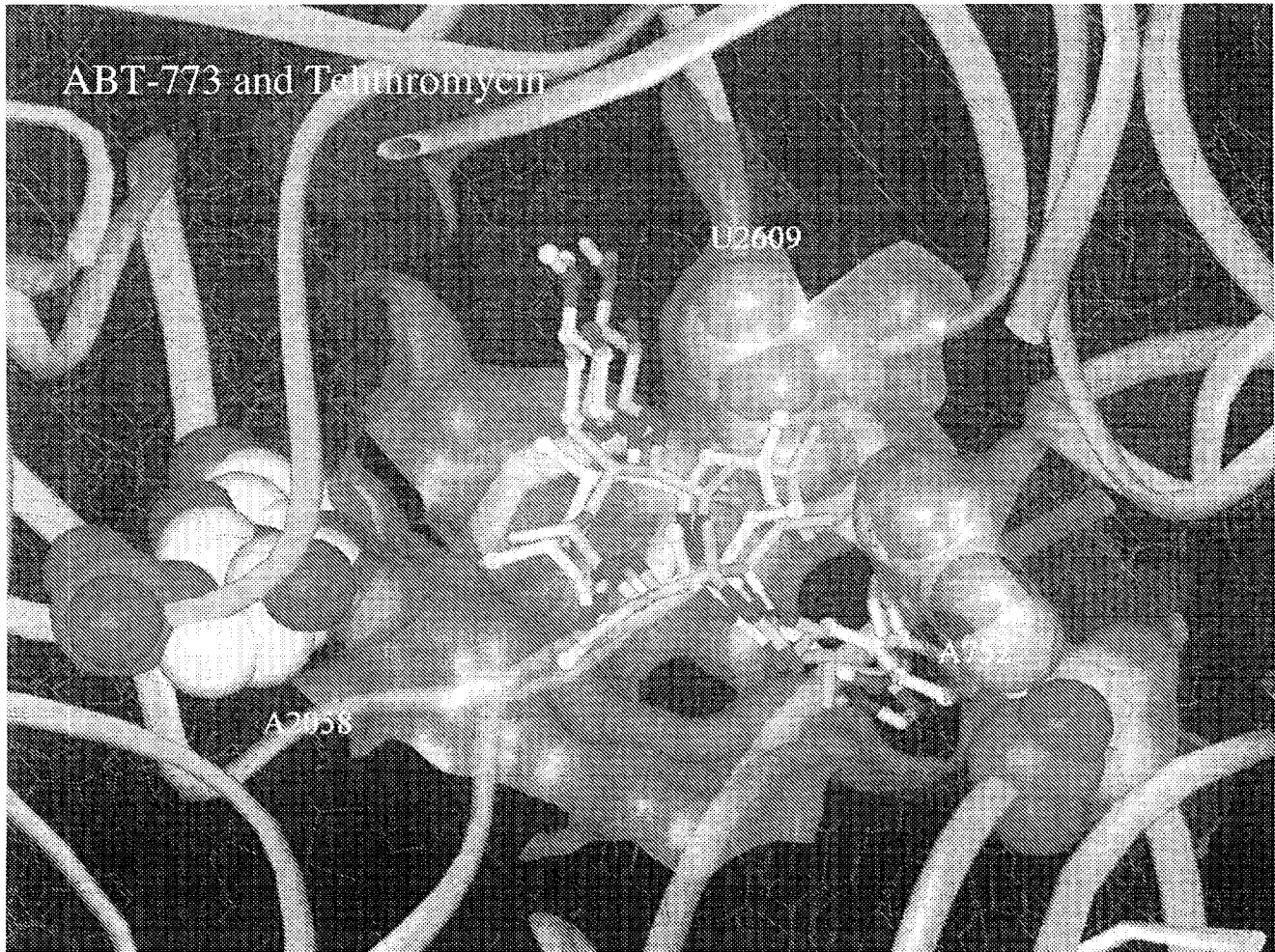
<sup>3</sup>Strigl et. al.2000. AAC.44:1112-1113



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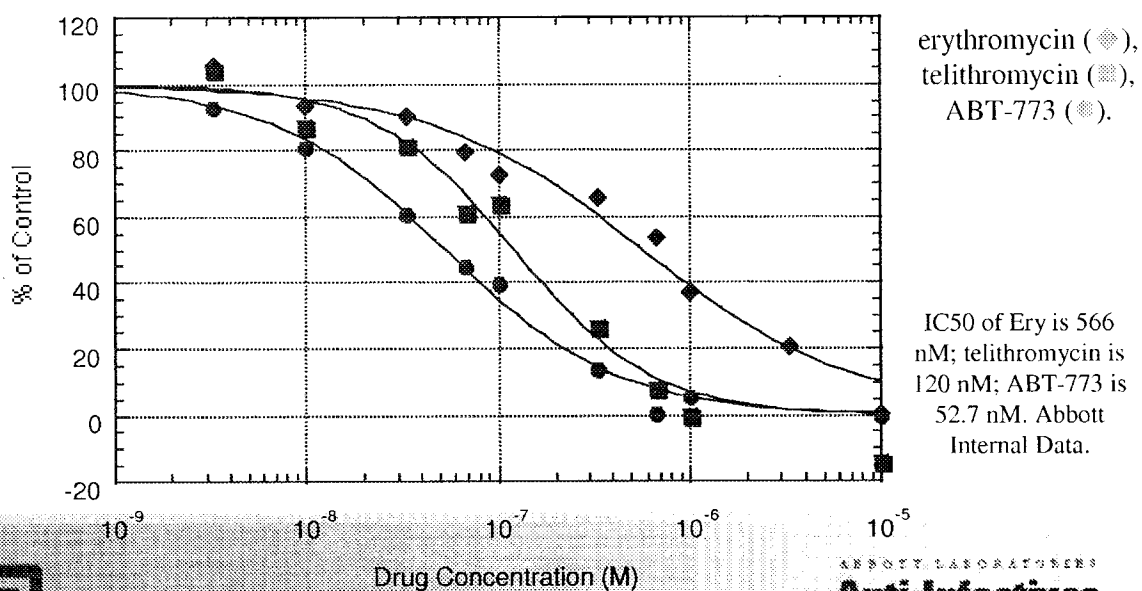


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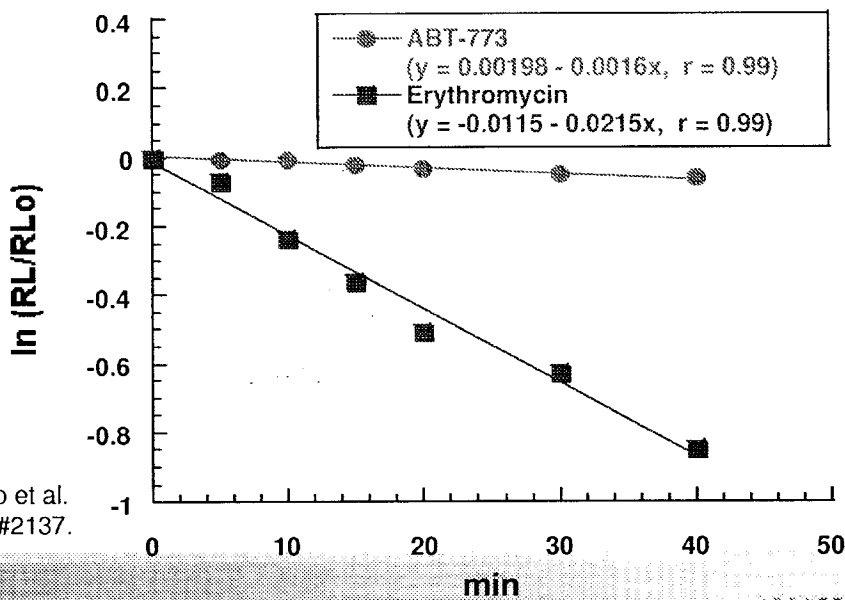
## Microbiology

Ribosome Binding, Susceptible *S. pneumoniae*



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## ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.  
ICAAC 1999, #2137.

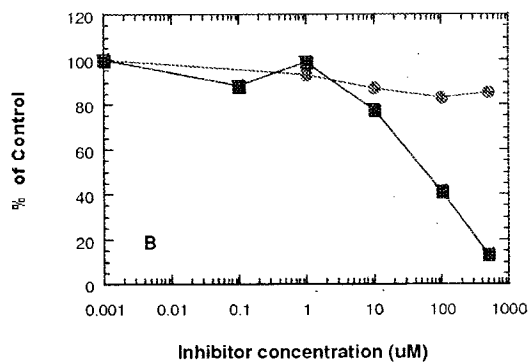
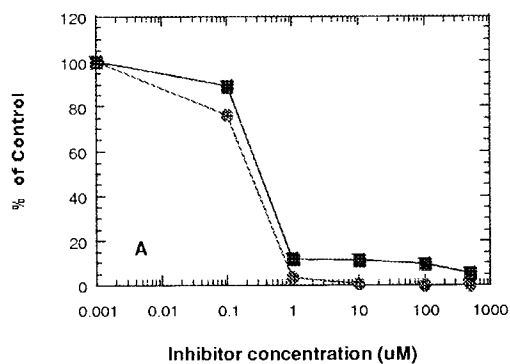


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**Microbiology**  
Inhibition of Transcription / Translation

S30 from susceptible *S. pneumoniae*

S30 from resistant *S. pneumoniae*



Red circles: erythromycin  
Blue squares: ABT-773



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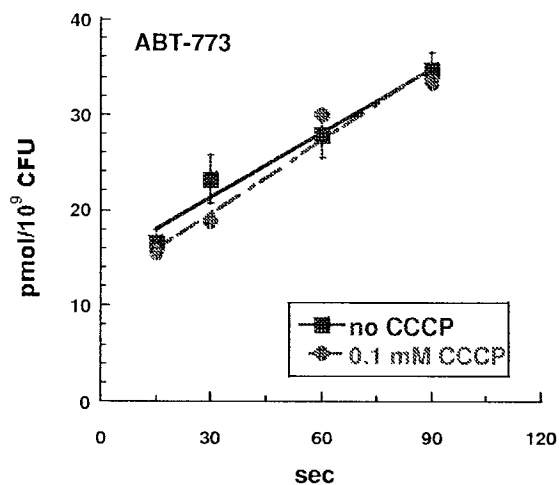
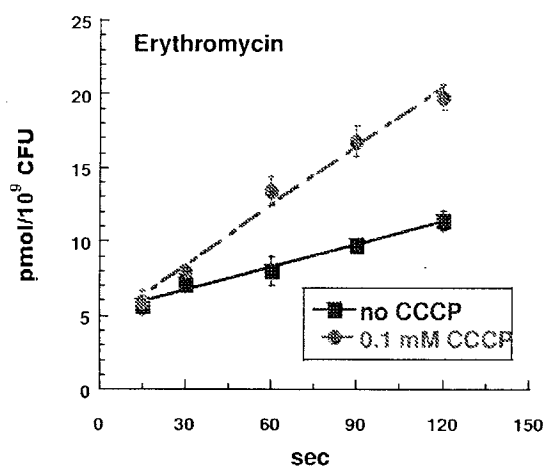
**Anti-Infectives**

Z Cao et. al. ICAAC 1999. Poster #2135



## Microbiology

### ABT-773 Accumulation in efflux<sup>+</sup> strain, with and without pump inhibitor (CCCP)



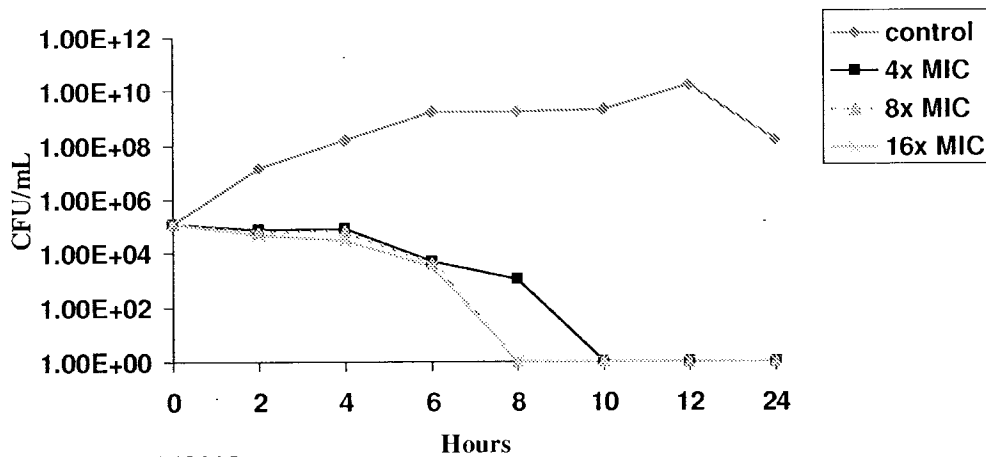
J. Capobianco et al. ICAAC 1999, #2137



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**Microbiology**  
*Bactericidal Activity, S. pneumoniae*

Susceptible *S. pneumoniae*; ABT-773 MIC 0.002 µg/ml

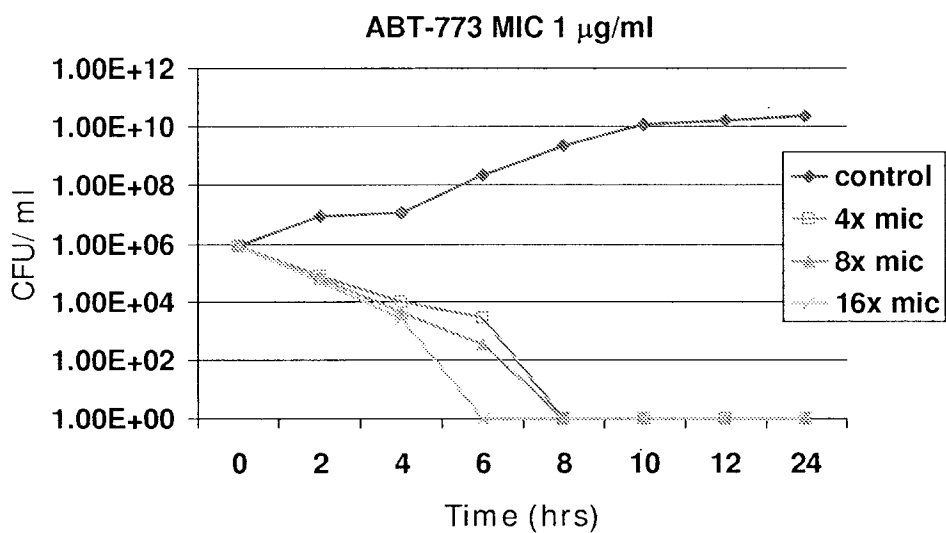


Ramer et al. ICAAC 2000



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**Microbiology**  
Bactericidal Activity, *H. influenzae*



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## **Microbiology**

### **Post Antibiotic Effect**

---

- After removal of drug the bacterial growth rate is inhibited
- Justification for dosing regimen such as QD vs. BID
- Addresses resistance development issues
- In vitro
  - *S. pneumoniae*
    - 8 strains
    - mean PAE ABT-773  $\geq$  6.1 hr
    - mean PAE ery 3.8hr
  - *H. influenzae*
    - 5 strains
    - mean PAE ABT-773  $\geq$  6.1 hr
    - mean ery PAE 3.8 hr



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**Microbiology**  
*Resistance Development*

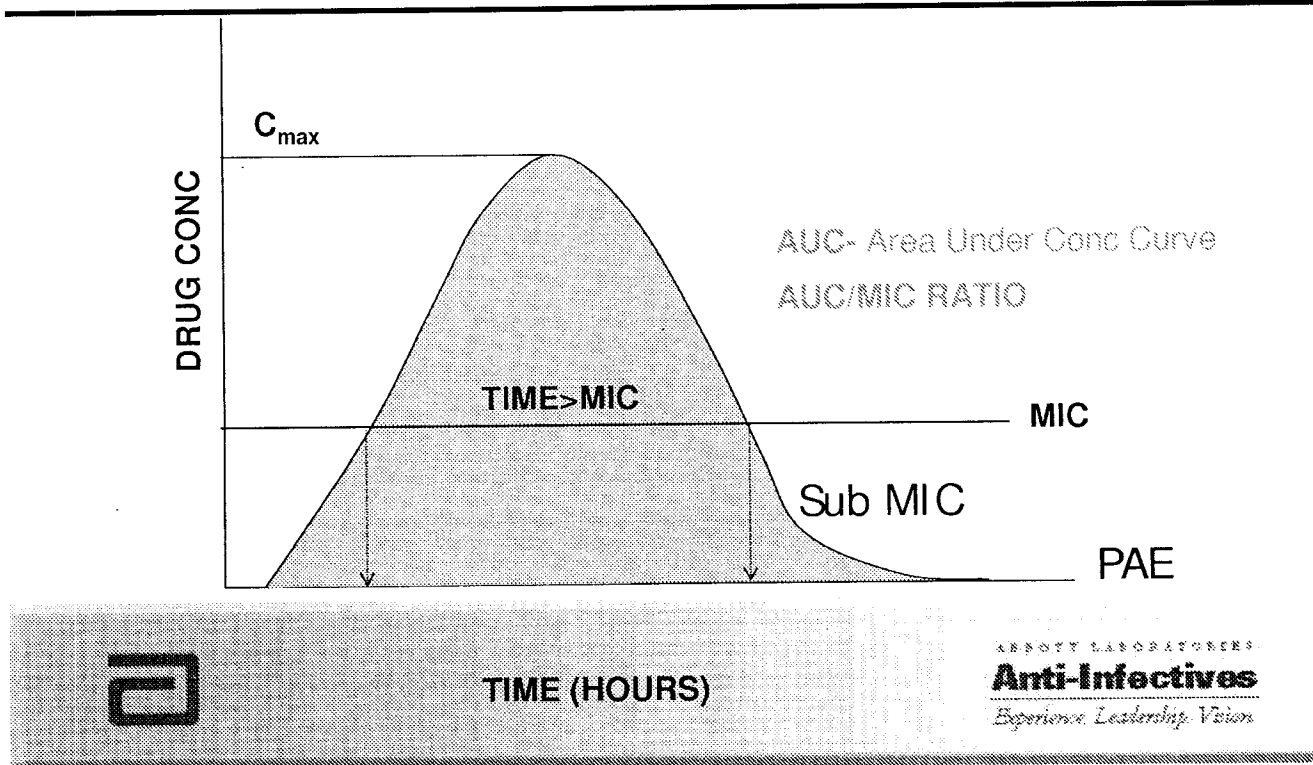
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- **Occur by mutation**
  - Quinolone resistance in GyrA and ParC
- **Acquired from another bacterium**
  - Methylase
  - Efflux
- ***S. pneumoniae***
  - In vitro single step mutation frequency (8XMIC)
    - 1 *S. pneumoniae* (S)  $<5.6 \times 10^{-10}$
    - 1 *S. pneumoniae* *mef*  $<2.6 \times 10^{-12}$
    - 2 *S. pneumoniae* *ermB*  $3.5 \times 10^{-10}$ – $9.4 \times 10^{-11}$
  - Mutation frequency for rifampicin (8XMIC)
    - 4 *S. pneumoniae*  $1.2 \times 10^{-6}$  to  $3.0 \times 10^{-7}$
  - No difference in mutation rate if macrolide resistant or susceptible
  - Low potential for resistance development



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**Microbiology**  
*Pharmacodynamic Parameters*



**Microbiology**  
*In vivo pharmacodynamics*

---

- Antibiotic exposure needed for efficacy against *S. pneumoniae* in animal models
  - AUC/MIC is best predictive parameter for ketolides
  - Rat lung model of pneumonia with *S. pneumoniae*
    - QD an AUC 0-24 ug.h/ml of 0.4-1.0 for an MIC<sub>90</sub> of 0.12
    - BID an AUC 0-24 ug.h/ml of 0.1-0.4 for an MIC<sub>90</sub> of 0.12
  - Lethal mouse model of pneumonia AUC 0-24 of <3-6 ug.h/ml



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**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model**

- *S. pneumoniae*
  - 6 macrolide susceptible , 8 macrolide resistant
  - $10^{5.8-7.4}$  CFU/ thigh
  - ABT-773 dose 0.023-24 mg/kg/day Q6 h
  - Net bacteriostatic effect over 24 hrs is measured

Andes, D.R. and W.A. Craig. ICAAC 2000.



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**Microbiology**  
*In vivo pharmacodynamics*

---

- **Neutropenic mouse thigh model- *S. pneumoniae***
  - 24hr AUC/MIC is best PK/PD predictor
  - Prolonged PAEs with concentration dependent killing
    - up to 11 hrs
  - Magnitude of AUC/MIC is not significantly altered by macrolide resistance with strains with MICs as high as 0.5µg/ml

Andes, D.R. and W.A. Craig. ICAAC 2000



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**Microbiology**  
*In vivo pharmacodynamics*

---

- **Mouse lethal pneumonia model**

- *S. pneumoniae*-2 strains
  - eryS
  - eryR
- immunocompetent mice
- infected with  $10^{4-5}$  CFU
- treatment 6 or 12 hr post-infection
- subcutaneous dosing
- BID treatment for 3 days

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.



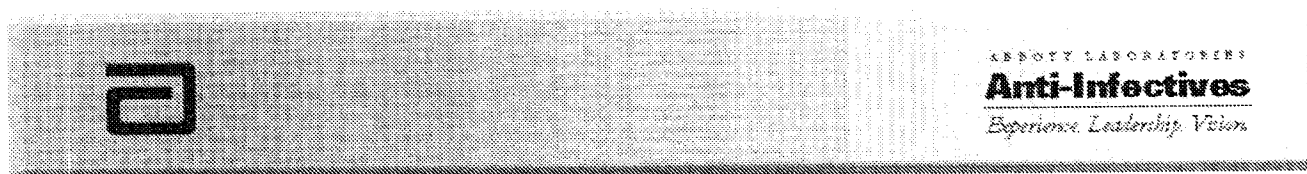
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**Microbiology**  
*In vivo pharmacodynamics*

---

- **vs. macrolide susceptible**
  - Ery/ABT-773 MIC 0.015/0.015 ug/ml
    - 100% survival with 3 days of treatment at s.c. 6.25mg/kg
- **vs. macrolide resistant**
  - Ery/ABT-773 MIC 1024/0.03 ug/ml
    - 93% survival with 3 days of treatment s.c. at 12.5 mg/kg
      - » infected mouse single dose 12.5 mg/kg- AUC 0-24 ug.h/ml 3.08+/- 0.32)

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.





**Microbiology**  
*In vivo pharmacodynamics*

---

- Suggests total daily AUC 0-24 ug.h/ml of <3- 6 is sufficient for pneumonia
  - ketolide is active vs macrolide resistant strain unlike erythromycin
  - no resistant mutants emerged vs ABT-773 but did for erythromycin

Azoulay-Dupuis, Bedos, Isturiz, Moine, Theron, Riex, Mohler, Carbon et. al. ICAAC 2000.

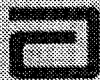


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**Microbiology**  
*Summary*

---

- Active vs. key respiratory pathogens including macrolide resistant streptococci
- Bactericidal
- Extended PAE
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome
  - Exposure of  $<1 \text{ ug.h/ml AUC}_{24}$  for mild to moderate pneumonia model and  $\text{AUC}_{24} \text{ ug.h/ml } <3-6$  for more severe model



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***Phase II Clinicals***  
*Joaquin Valdes*

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# PART 4

**Phase II Clinicals**  
*Program Summary*

Study	Study Drug Dose/Duration	Patient Numbers/location
M99-048 Phase IIb, Double blind Acute Bacterial Exacerbation of Chronic Bronchitis	ABT-773 150, 300 or 600 mg OD Duration: 5 days	N = 384 US, Germany, France, Italy, Spain, UK, Chile
M99-053 Phase IIb, Double-blind Acute Sinusitis	ABT-773 150, 300, or 600 mg OD Duration: 10 days	N = 292 US, Finland, Greece, Chile
M99-054 Phase IIb, Double-blind Community Acquired Pneumonia	ABT-773 300 or 600 mg OD Duration: 7 days	N = 187 US, Germany, France, Italy, Spain, Poland, South Africa



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***Acute Bacterial Exacerbation of Chronic Bronchitis***  
***M99-048***  
***Clinical Response***

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	88% (49/56)	94% (59/63)
Clin Eval	87% (98/113)	90% (105/117)	90% (101/112)
ITT	85% (104/123)	83% (107/129)	83% (106/128)



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**Acute Bacterial Exacerbation of Chronic Bronchitis**  
**M99-048**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	83% (10/12)	90% (9/10)	100% (13/13)
<i>M. catarrhalis</i>	80% (8/10)	92% (12/13)	91% (10/11)
<i>H. influenzae</i>	94% (17/18)	89% (17/19)	83% (19/23)
Overall	88% (35/40)	91% (38/42)	89% (42/47)



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**Acute Bacterial Exacerbations of Chronic Bronchitis**  
**M99-048**  
**Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
Taste Perversion	6% (7/126)	19% (25/129)	29% (37/129)
Diarrhea	13% (16/126)	12% (15/129)	21% (27/129)
Nausea	7% (9/126)	13% (17/129)	30% (38/129)
Vomiting	2% (3/126)	3% (4/129)	11% (14/129)
Nausea and Vomiting	0	<1% (1/129)	4% (5/129)
Abdominal Pain	4% (5/126)	4% (5/129)	4% (5/129)

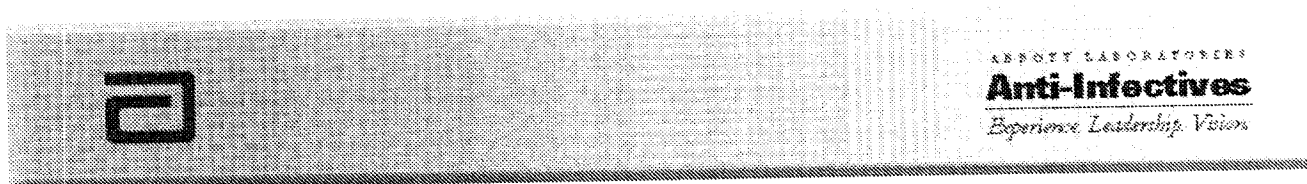


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**Community-Acquired Pneumonia  
M99-054  
Clinical Response**

	300 mg	600 mg
Clin and Bact. Eval	92% (54/59)	82% (47/57)
Clin Eval	92% (72/78)	80% (56/70)
ITT	84% (80/95)	73% (65/89)



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**Community-Acquired Pneumonia**  
**M99-054**  
**Radiographic Response**

**(Resolution/Improvement)**

	300 mg	600 mg
Clin and Bact. Eval	100% (56/56)	89% (48/54)
Clin Eval	99% (73/74)	88% (57/65)
ITT	84% (80/95)	72% (64/89)



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**Community-Acquired Pneumonia**  
**M99-054**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	300 mg		600 mg	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)
<i>C. pneumoniae</i>	95%	19/20)	79%	(19/24)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)
Overall	91%	(63/69)	81%	(57/70)



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**Community-Acquired Pneumonia**  
**M99-054**  
**Adverse Events**

**All Adverse Events**

	300mg		600mg	
GI and Taste				
Taste Perversion	17%	(16/95)	26%	(24/92)
Diarrhea	14%	(13/95)	19%	(17/92)
Nausea	12%	(11/95)	22%	(20/92)
Vomiting	10%	(9/95)	15%	(14/92)



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**Sinusitis**  
**M99-053**  
**Clinical Response**

	150 mg	300 mg	600 mg
Clin Eval	89% (70/79)	83% (70/84)	71% (59/83)
ITT	82% (72/88)	80% (72/90)	67% (59/88)

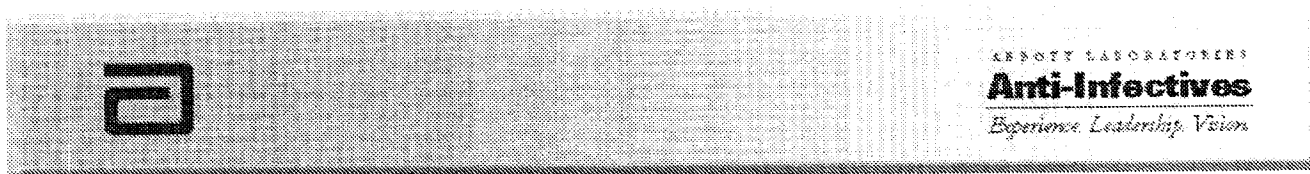


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**Sinusitis  
M99-053  
Radiographic Response**

**(Resolution/Improvement)**

	150 mg	300 mg	600 mg
Clin Eval	86% (68/79)	86% (71/83)	78% (59/76)
ITT	81% (71/88)	81% (73/90)	67% (59/88)



**Sinusitis**  
**M99-053**  
**Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	3/3	8/8	9/12
<i>M. catarrhalis</i>	8/9	3/4	4/4
<i>H. influenzae</i>	3/5	7/7	5/7
<i>S. aureus</i>	1/1	1/1	3/4



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**Sinusitis**  
**M99-053**  
**Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
GI and Taste			
Taste Perversion	1% (1/97)	14% (14/98)	27% (26/97)
Diarrhea	6% (6/97)	6% (6/98)	17% (16/97)
Nausea	3% (3/97)	12% (12/98)	26% (25/97)
Vomiting	1% (1/97)	6% (6/98)	17% (16/97)



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*Insert cure/erad/AE summary table*

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ABBT205176

**ABECB, CAP, AMS**  
**M99-048, M99-054, M99-053**  
**Clinical Response**

---

	150 mg	300 mg	600 mg
Clin and Bact. Eval	84% (42/50)	90% (103/115)	88% (106/120)
Clin Eval	88% (168/193)	88% (247/279)	81% (216/265)
ITT	83% (176/211)	82% (259/314)	75% (230/305)

---



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**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Bacteriological Response**

**Clinically and Bacteriologically Evaluable**

	150mg	300mg	600mg
<i>S. pneumoniae</i>	87% (13/15)	91% (30/33)	91% (29/32)
<i>M. catarrhalis</i>	84% (16/19)	84% (21/25)	84% (16/19)
<i>H. influenzae</i>	87% (20/23)	94% (33/35)	77% (37/48)
Overall	86% (49/57)	90% (84/93)	83% (82/99)



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**ABECB, CAP, AMS  
M99-048, M99-054, M99-053  
Adverse Events**

**All Adverse Events**

	150 mg	300 mg	600 mg
<b>GI and Taste</b>			
<b>Taste Perversion</b>	<b>4%</b> (8/223)	<b>17%</b> (55/322)	<b>27%</b> (87/318)
<b>Diarrhea</b>	<b>10%</b> (22/223)	<b>11%</b> (34/322)	<b>19%</b> (60/318)
<b>Nausea</b>	<b>5%</b> (12/223)	<b>12%</b> (40/322)	<b>26%</b> (83/318)
<b>Vomiting</b>	<b>2%</b> (4/223)	<b>6%</b> (19/322)	<b>14%</b> (44/318)

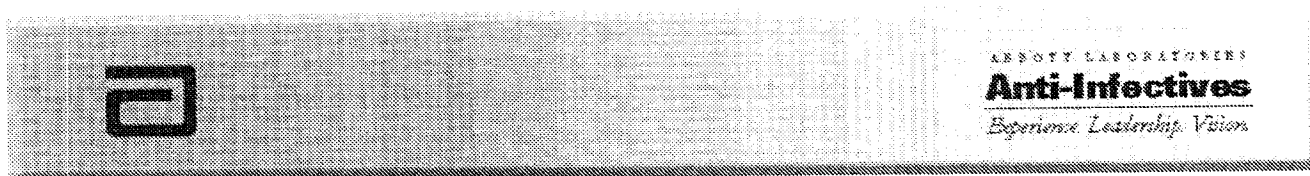


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### ***Phase II summary***

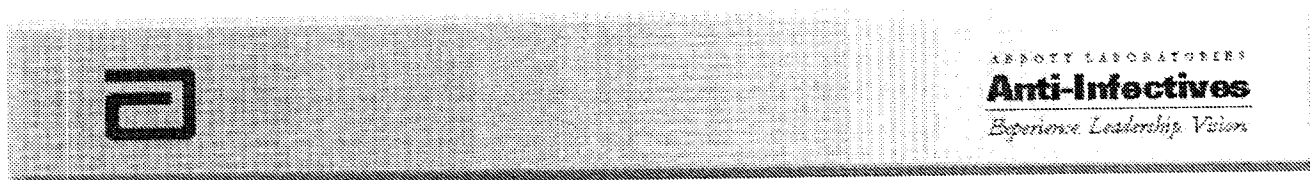
---

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD will be evaluated in comparative studies of ABECB and pharyngitis in phase III
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS



---

***Phase III Clinical Program  
Joaquin Valdes***



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### ***Proposed Indications and Treatment Duration***

<b>Infection</b>	<b>Dosage (QID)</b>	<b>Duration (days)</b>
Pharyngitis/Tonsillitis due to <i>S. pyogenes</i> *	150 mg	5
Acute bacterial sinusitis due to		
<i>H. influenzae</i>	150 mg (or BID)	10
<i>M. catarrhalis</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10
Acute bacterial exacerbation of chronic bronchitis due to		
<i>H. influenzae</i>	150 mg	5
<i>H. parainfluenzae</i>	150 mg	5
<i>M. catarrhalis</i>	150 mg	5
<i>S. pneumoniae</i> **	150 mg	5
Community-acquired pneumonia due to		
<i>C. pneumoniae</i>	150 mg (or BID)	10
<i>H. influenzae</i>	150 mg (or BID)	10
<i>L. pneumophila</i>	150 mg (or BID)	10
<i>M. pneumoniae</i>	150 mg (or BID)	10
<i>S. pneumoniae</i> **	150 mg (or BID)	10

\* Including macrolide-resistant strains.

\*\* Including penicillin-resistant and macrolide-resistant strains.



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**Phase 3 Studies****Studies starting in year 2000:**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-223	Pharyngitis	150 mg QD 5 days	Penicillin V	260	US (IND)
M00-222	Pharyngitis	150 mg QD 5 days	Penicillin V	260	EU (Non-IND)
M00-216	ABECB	150 mg QD 5 days	Azithromycin	300	US, Canada IND
M00-217	ABECB	150 mg QD 5 days	Levofloxacin	250	EU (Non-IND)



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**Phase 3 Studies****Studies starting in year 2000 (Cont.):**

Study	Indication	ABT-773 Regimen	Comparator	Number ABT-773 Subjects	Location
M00-225	Sinusitis	150 mg QD vs. 150 mg BID 10 days	None	600	US, EU (IND)
M00-219	CAP	150 mg QD vs. 150 mg BID 10 days	None	800	US, Canada, EU (IND)



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**Phase 3 Studies****Studies starting in year 2001:**

Study	Indication	Comparator	Number ABT-773 Subjects	Location
M00-221	CAP	Levofloxacin	225	US, Canada (IND)
M00-220	CAP	Augmentin or Amoxicillin	250	EU (Non-IND)
M00-226	Sinusitis	Augmentin	225	US, Canada (IND)
M00-218	Sinusitis	Augmentin or Quinolone	250	EU (Non-IND)



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**Proposed Claim for Macrolide or  
Penicillin Resistant Bacteria and Atypicals**

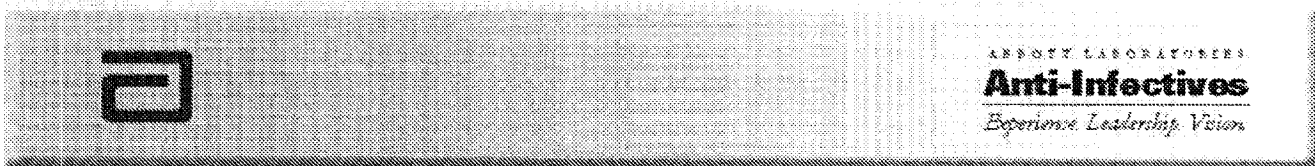
<b>Claim</b>	<b>Supporting Data</b>
Macrolide-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Penicillin-resistant <i>S. pneumoniae</i>	15 isolates worldwide from Phase 3 CAP and ABECB
Macrolide-resistant <i>S. pyogenes</i>	15 isolates worldwide from Phase 3 pharyngitis
Atypicals; <i>C. pneumoniae</i> , <i>M. pneumoniae</i> , <i>Legionella spp.</i>	15 isolates worldwide per organism (include positive serology) from Phase 3 CAP



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***Bulk Drug Manufacturing***  
*Ashok Bhatia*

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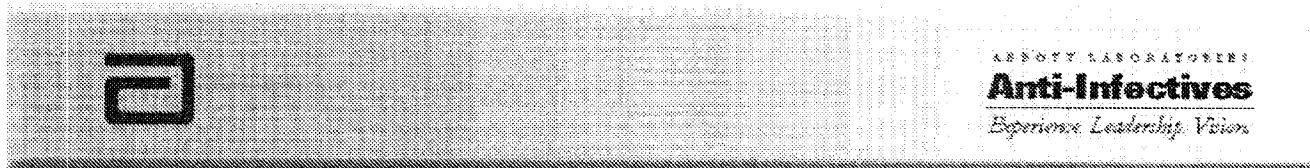
ABBT205187

***Bulk Drug Manufacturing***  
***Agenda***

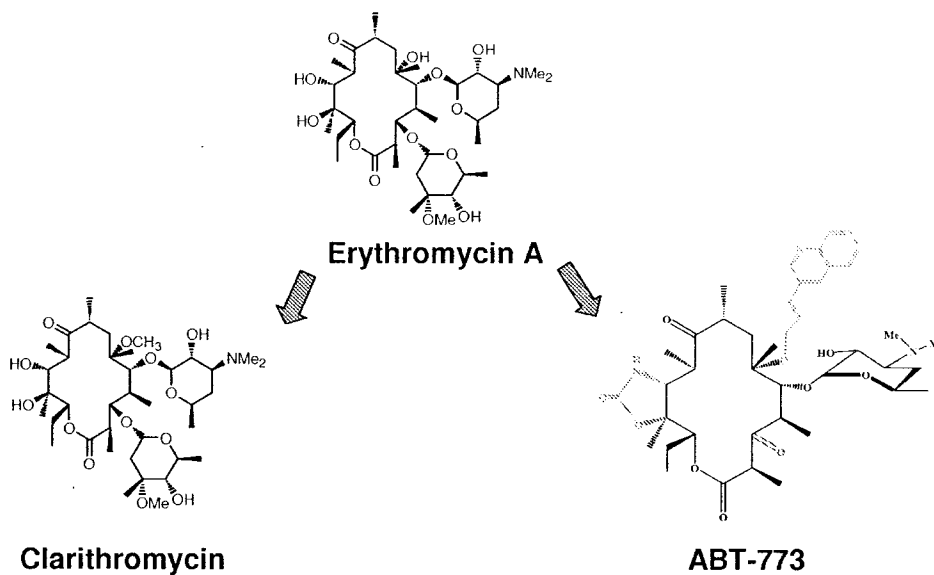
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**Agenda**

- Chemistry
- Process Strategy and Review
- Cost Review and Projection

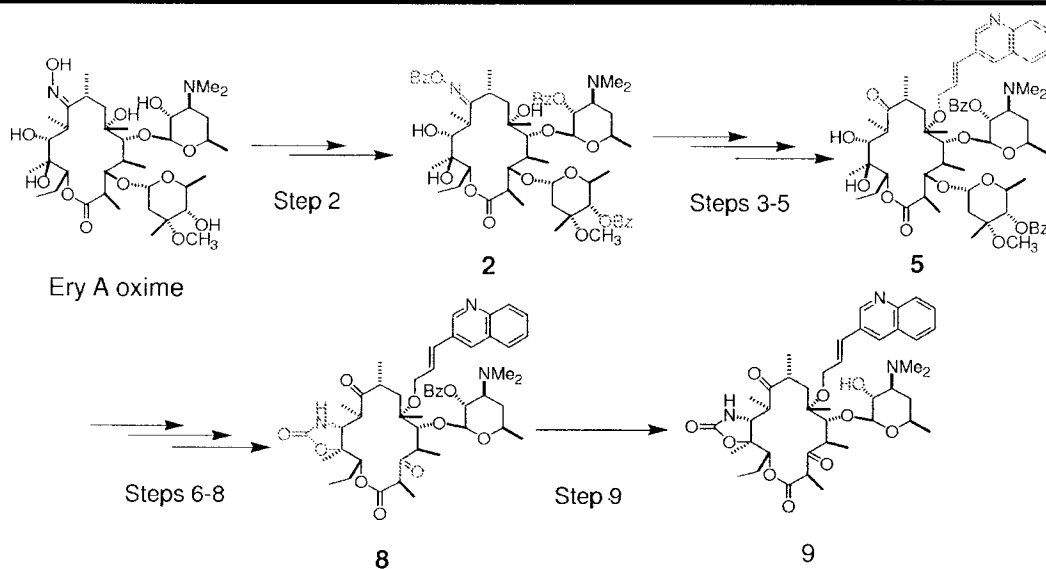


**Bulk Drug Manufacturing**  
**Macrolide Structures**



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**Bulk Drug Manufacturing**  
**ABT-773 Synthesis**

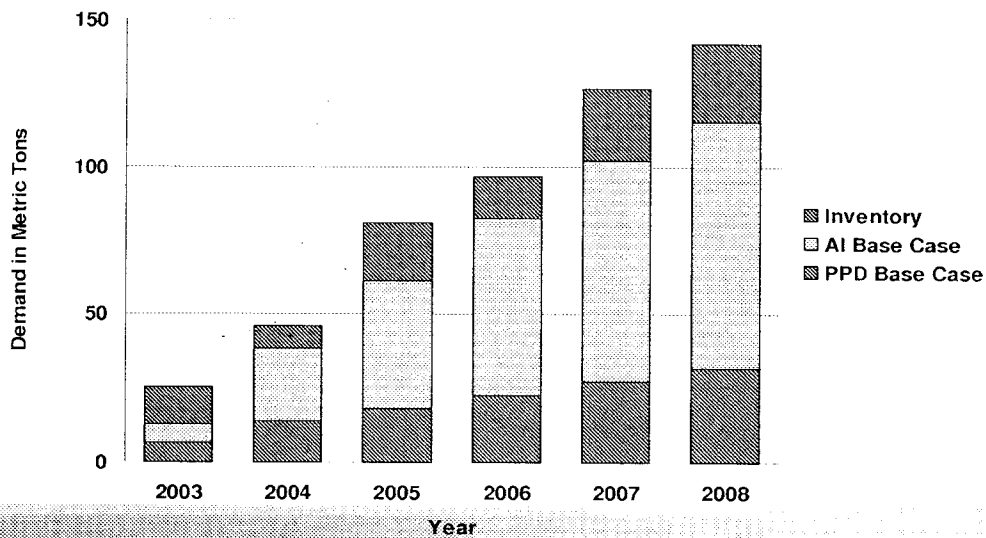


ABT - 773

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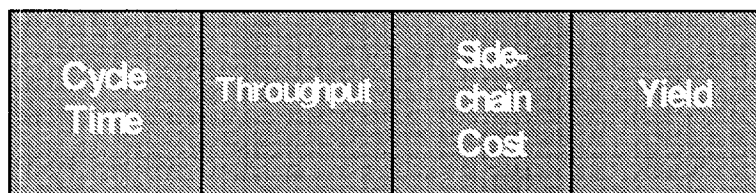
**Bulk Drug Manufacturing**  
*Drug Substance Demand*

**ABT-773 Bulk Demand - Consolidated LRP**



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**Bulk Drug Manufacturing Process Improvements**

**Enhanced  
Process  
Efficiency**

	1998	1999	2000
CycleTime (Days)	53	35	30
Throughput Batch Size Manuf. Sites	100 kg 1	175 kg 5	350 kg 5
Side-chain Cost	\$2500/kg	\$1100/kg	\$950/kg
Yield (%)	18	21	28

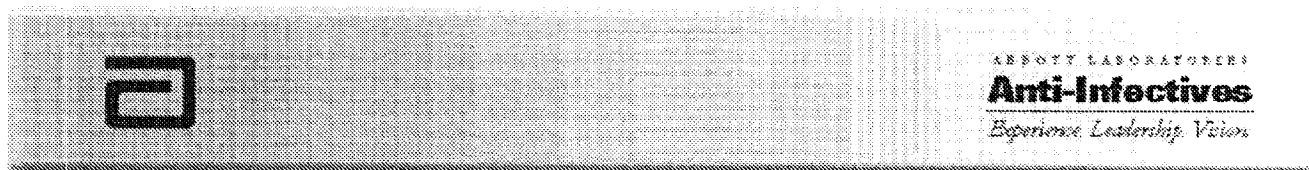


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# PART 5

**Bulk Drug Manufacturing**  
*Comparison of Projected & Actual Demand/Cost*

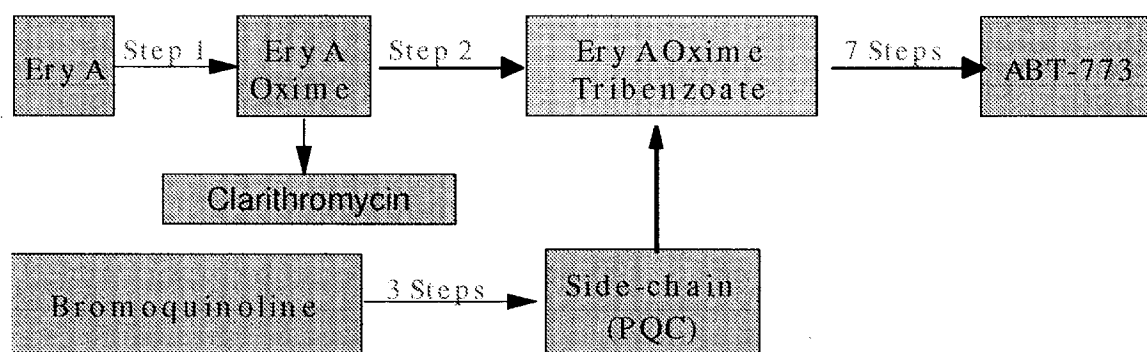
		1999	2000	2001
Bulk Drug	Demand (kg)	1,400	2,520	1,675
	Actual (kg)	1,488	2,815	
Cost/kg	Projected (\$)	\$10,000	\$6,500	\$5,000
	Actual (\$)	\$7,800	\$5,400 (est.)	



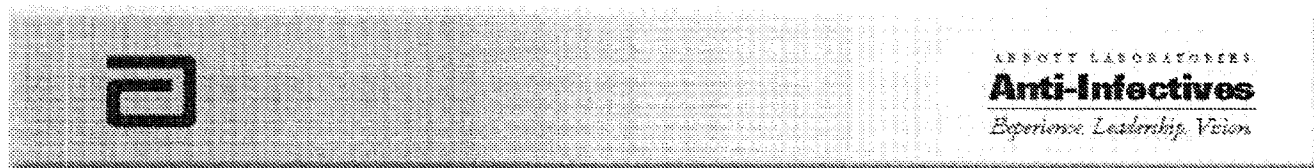
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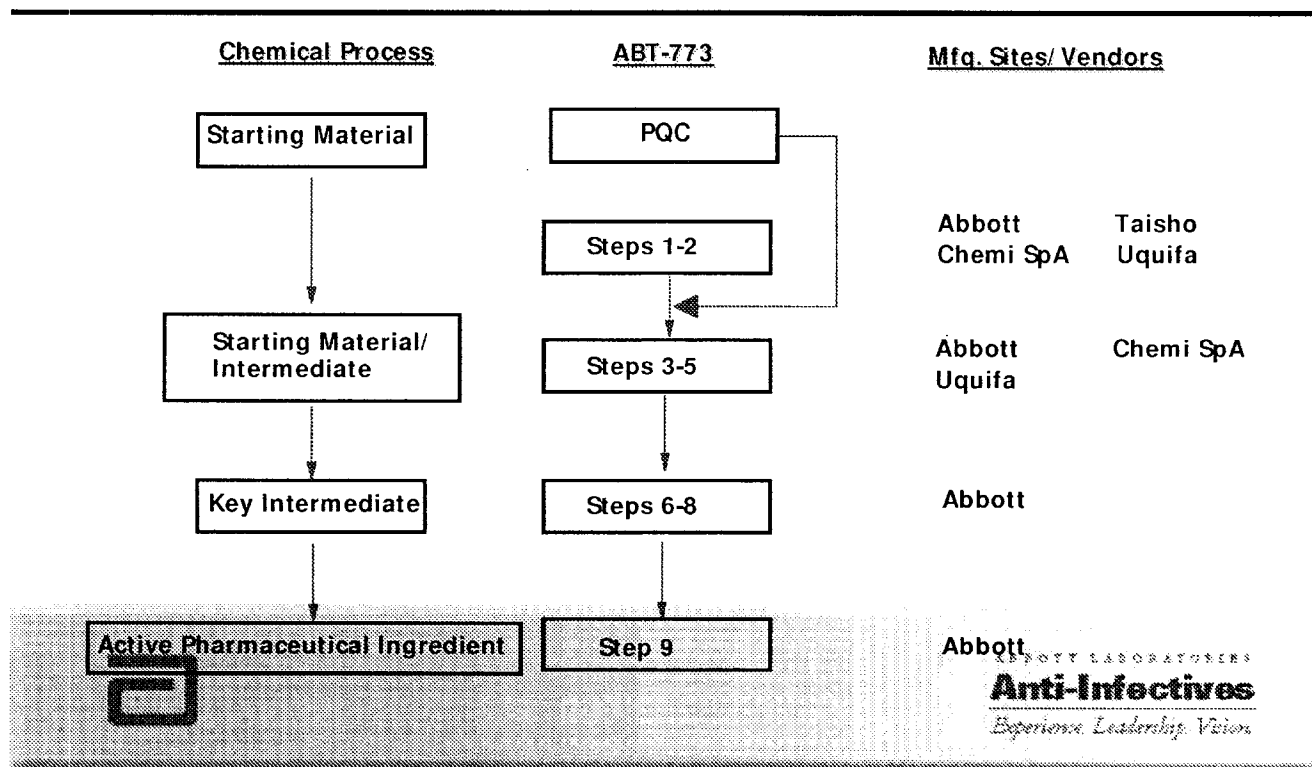
## Bulk Drug Manufacturing Synthesis



- Bromoquinoline sources from India and China
- Side-chain outsourced from India and Europe
- Intermediates up to Step 5 outsourced/internal



**Bulk Drug Manufacturing**  
*Manufacturing Strategy: Starting Materials & Intermediates*



***Bulk Drug Manufacturing***  
***Step 5 as Starting Material***

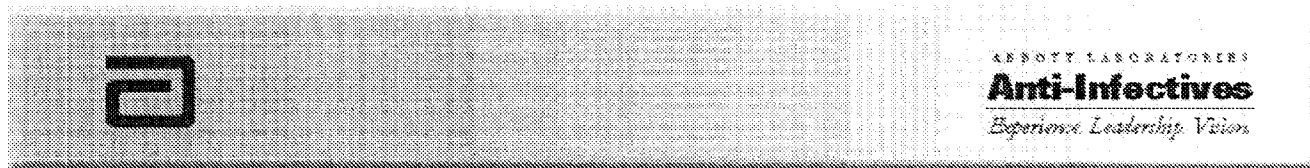
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**Criteria:**

- Readily available at commercial scale
- Structure incorporated in Drug Substance molecule
- Well-characterized and known impurity profile
- Prepared by known methods

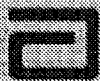
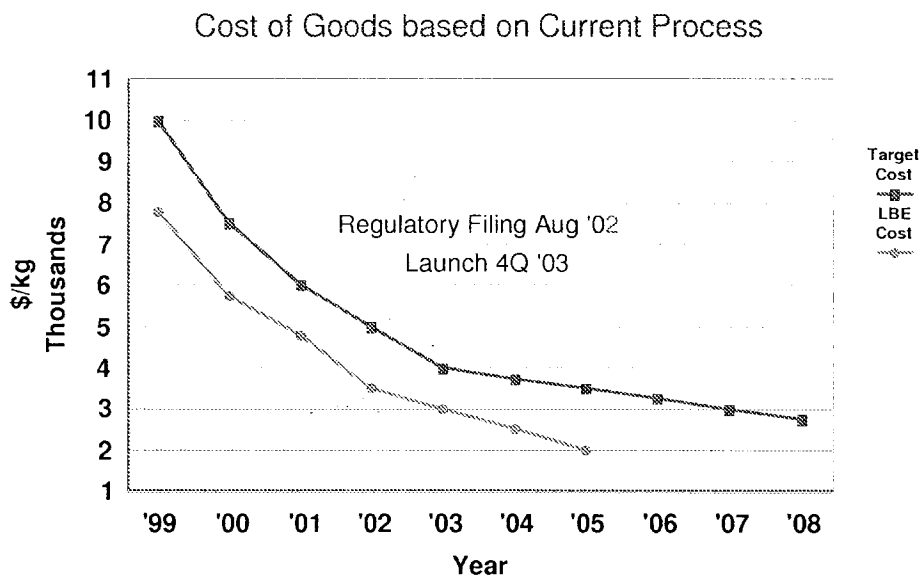
**Advantages:**

- Commercial flexibility – additional manufacturers
- Process improvements (changes) without FDA prior approval
- Cost advantage



## Bulk Drug Manufacturing

Projected Bulk Drug Costs



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***Bulk Drug Manufacturing***  
***Projected Annual Capacity, Single Site***

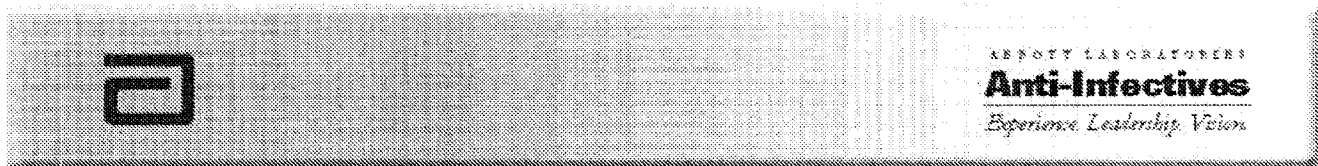
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Bldg C7A/ NC	15MT
Bldgs C17 and C7A/ NC	50MT

**Alternative strategies:**

**Step 8 at vendor site(s)**

**Manufacturing in Abbott, Puerto Rico**



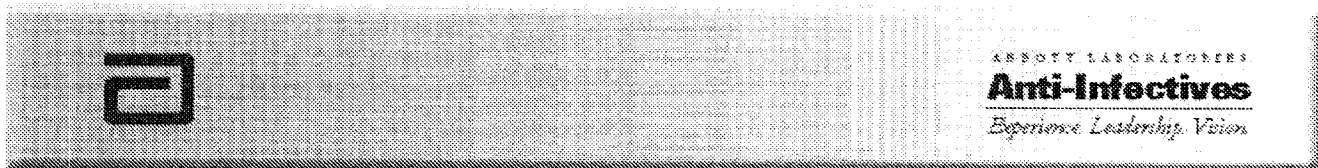


***Bulk Drug Manufacturing***  
*Summary*

---

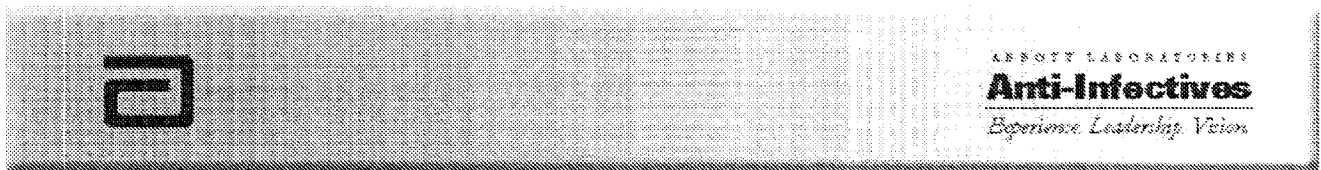
**Summary**

- A viable process developed for commercial launch
- On track to achieve commercial target cost
- Identified strategies to meet long term bulk substance demand



## *Tablet Key Issues*

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**QT Prolongation**  
*Dave Morris*

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ABBT20520

### *Summary of ECG*

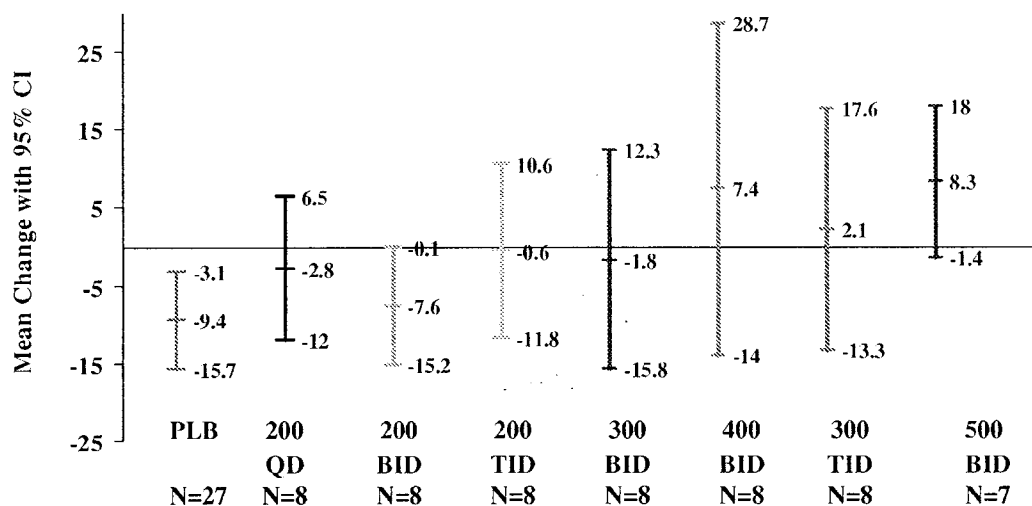
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- A possible dose effect in Phase I at total daily dose  $\geq 800\text{mg}$ .
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole.
- No concentration response in Phase I studies ( $\leq 300\text{mg}$ ).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies.
- Will continue to monitor QT in Phase III programs.



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**Mean Change of QTC  
(Multiple Rising Dose Study)**

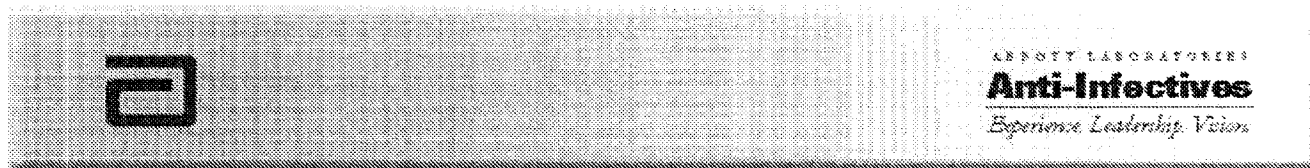


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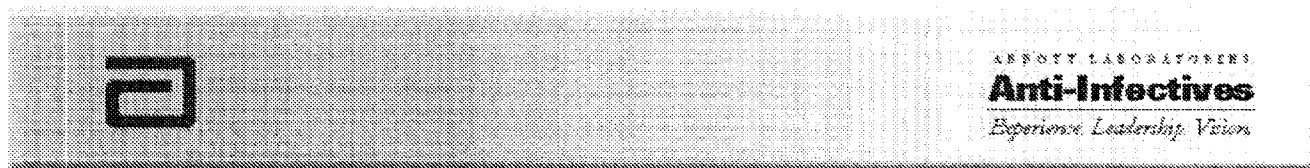
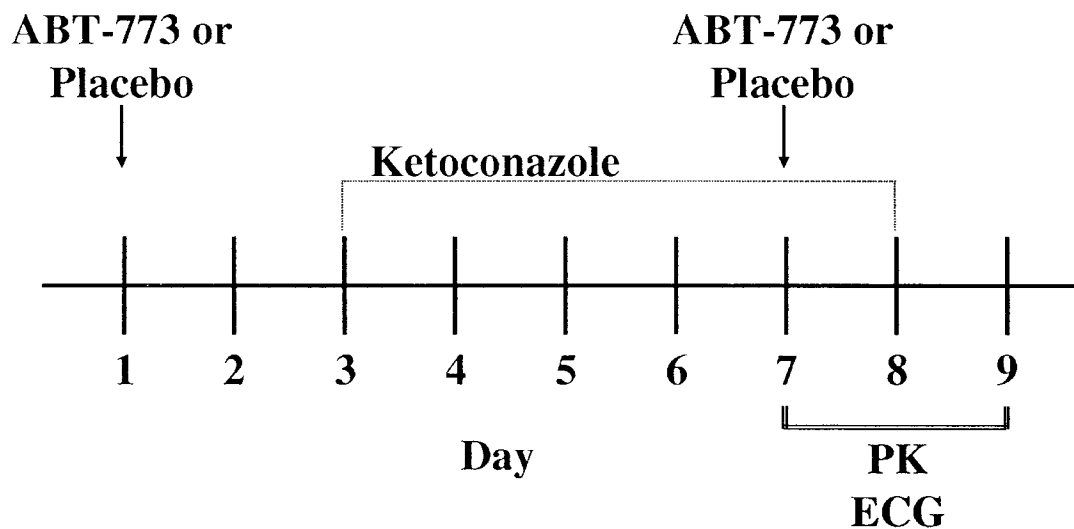
### *Multiple Rising Dose Study*

---

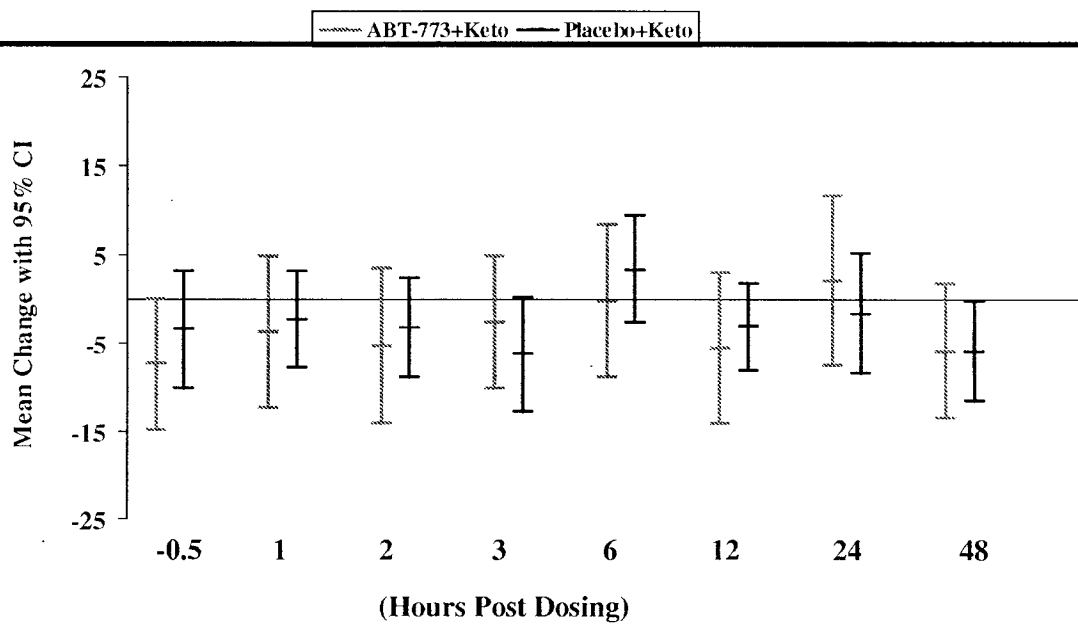
- No subject had QTc increase > 60 msec
- 3 subjects had QTc increase 30-60 msec ( $\geq 800$ mg/day)
- No subject had QTc of >500 msec
- No syncope observed



### *Ketoconazole Interaction Study*



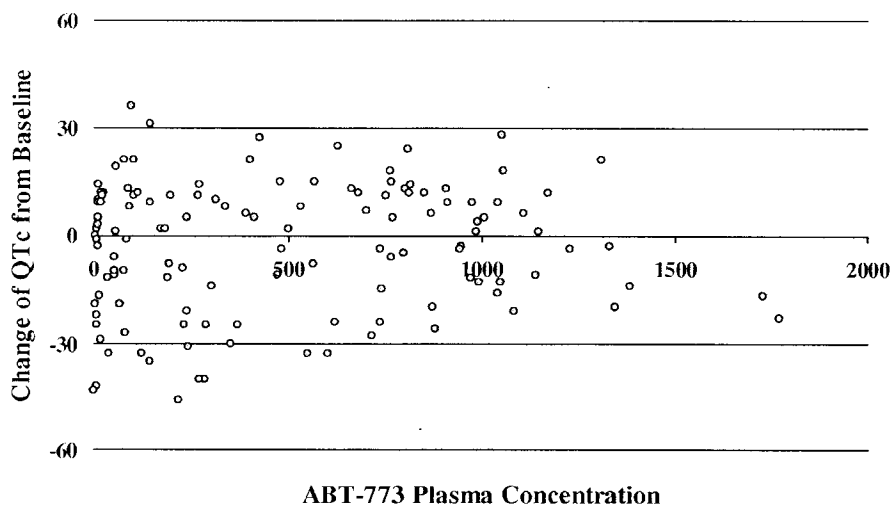
Mean Change of QTC  
(Ketoconazole Interaction Study - N = 18)



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Ketoconazole Interaction Study

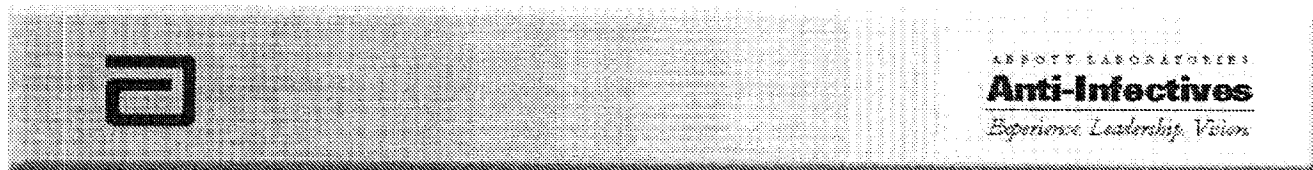


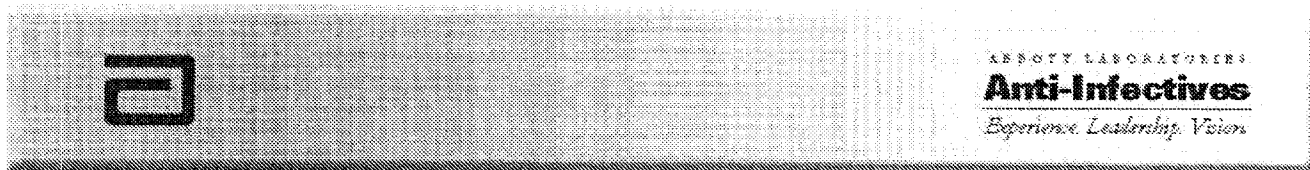
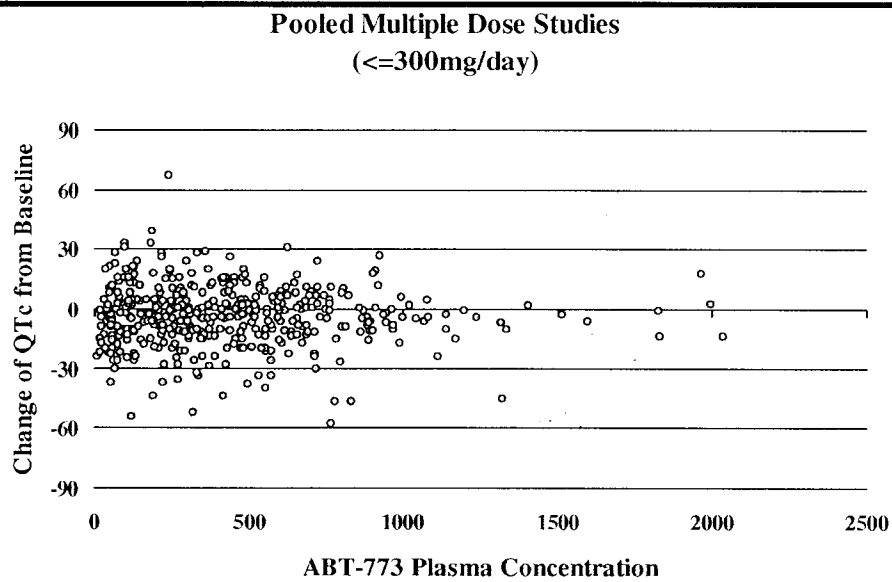
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### *Ketoconazole Interaction Study*

---

- No subject had QTc increase > 60 msec.
- 2 subjects had QTc increase of 30-60 msec.
- No subject had QTc of >500 msec
- No syncope observed





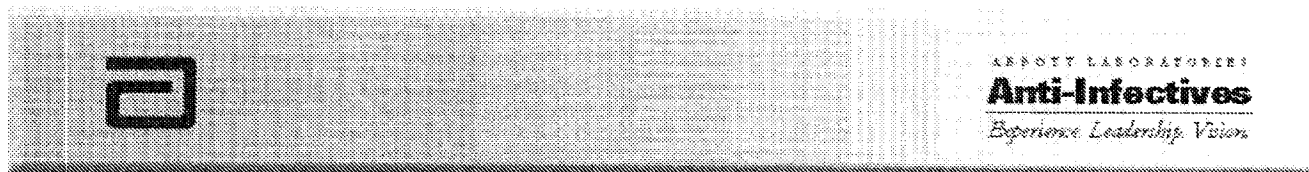
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ABB205206

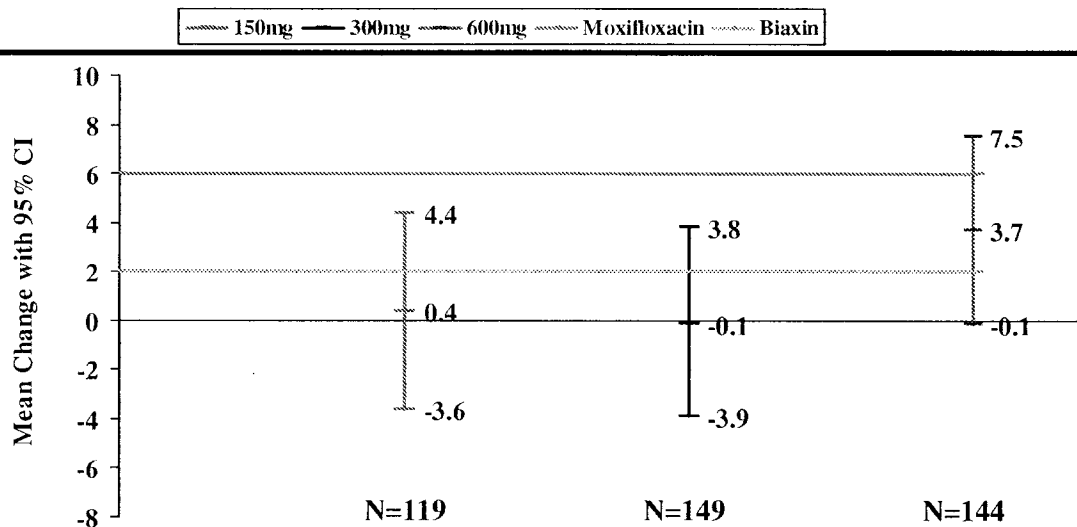
### *All Phase I Studies*

---

- Total of 11 syncopes reported
  - 5 were pre-dosing
  - 6 were post-dosing
- All associated with blood draw



Mean Change of QTc from Pretreatment to During Treatment  
(Phase IIB - Based on Cardiologist Reading)



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### *Phase IIA/B*

---

- 2 syncopes reported
  - 1 was immediately upon first dose on Day 1 (600mg QD)
  - 1 was 7 days post last dose (100mg TID)



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***Liver Function***  
***Dave Morris***

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### ***LFT Summary***

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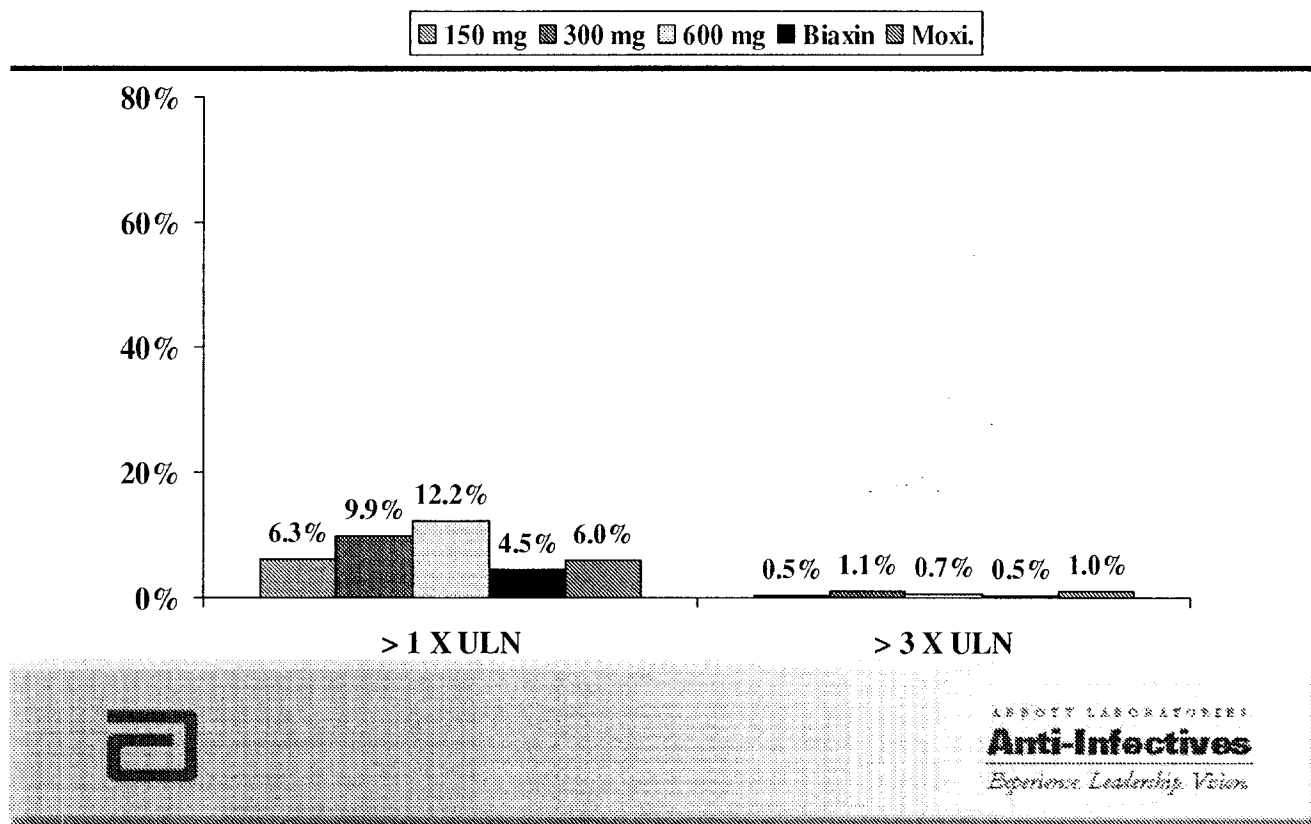
- No evidence of LFT issue in Western subjects.
- No consistent evidence of dose response.
- Japanese bridging study results should be confirmed.
- Will continue to monitor LFT in Phase III programs.



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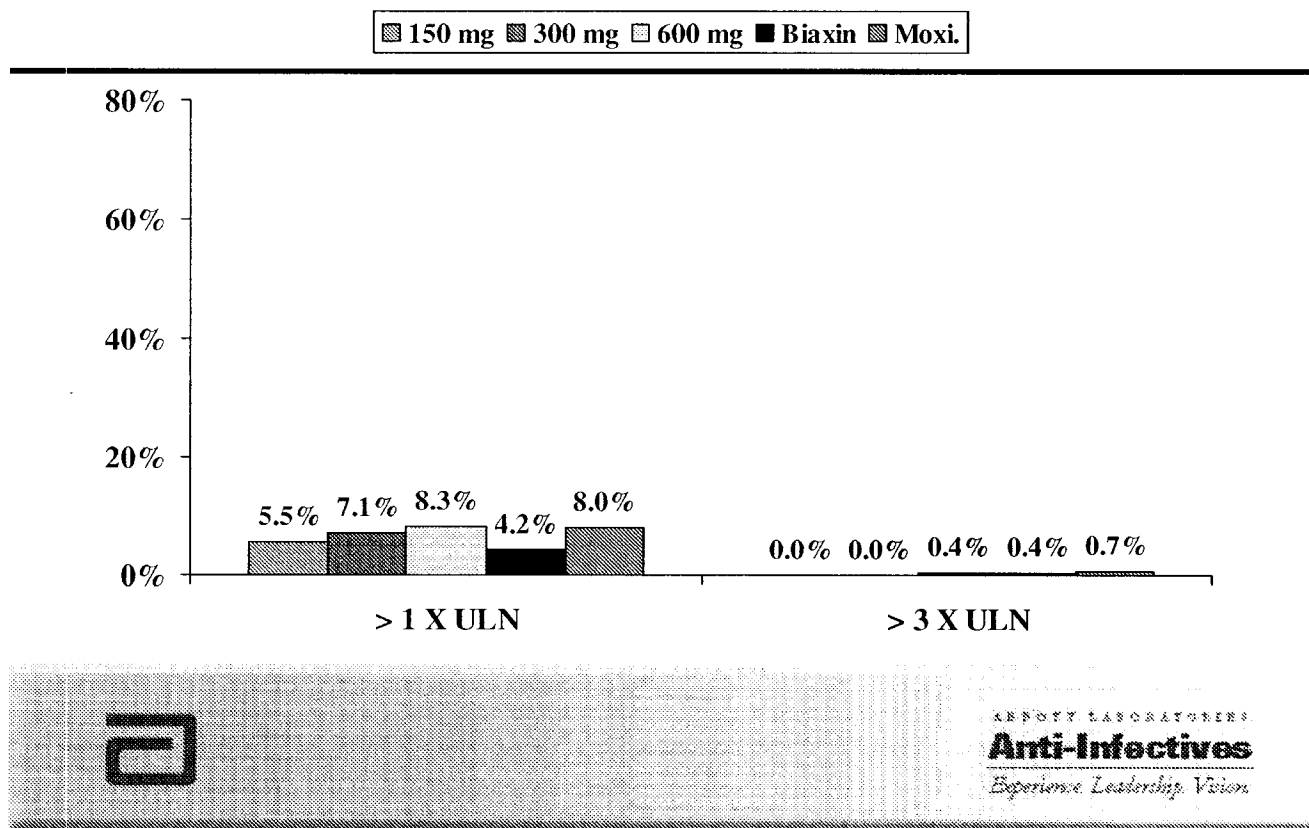
## Incidence Rate of SGPT Abnormalities



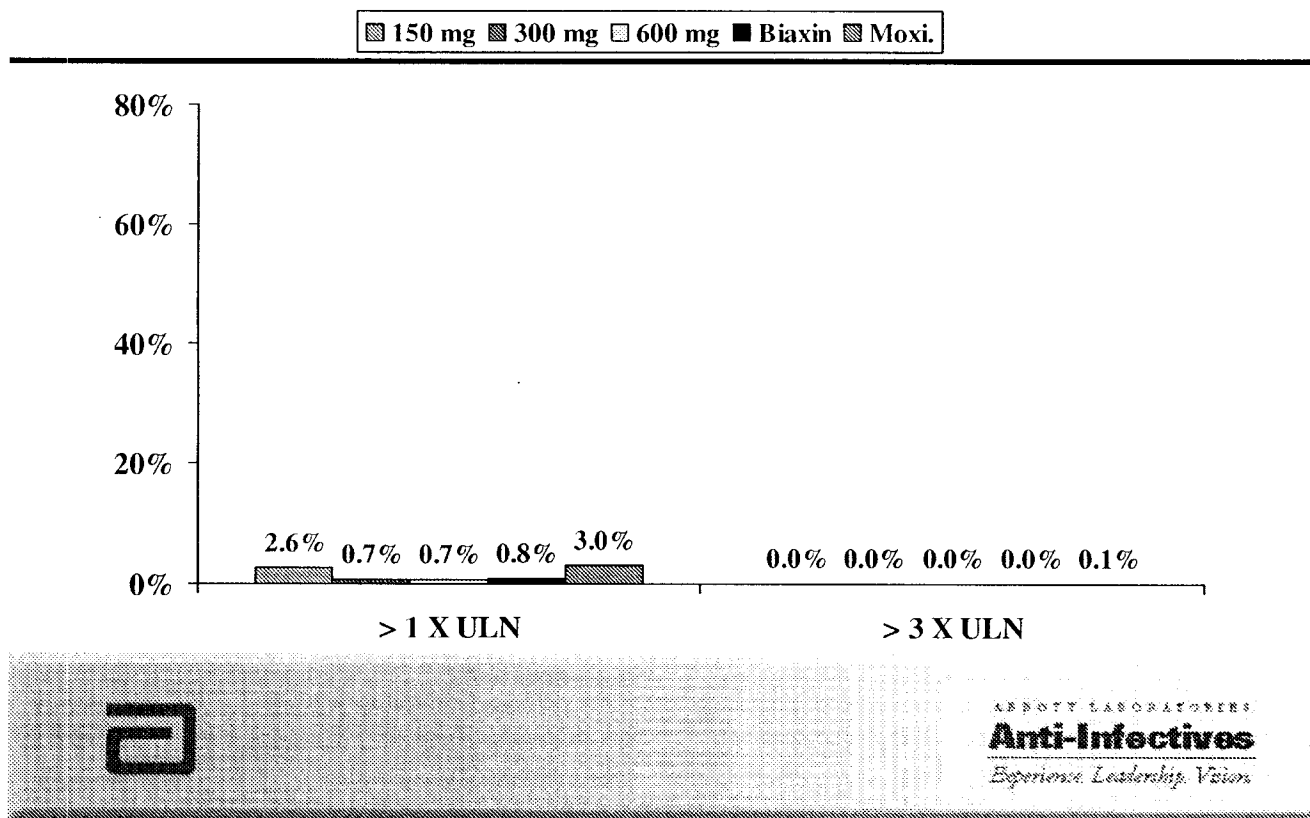
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ABBT20521!

## Incidence Rate of SGOT Abnormalities



## Incidence Rate of Bilirubin Abnormalities



**Very high LFT Results: Phase II**

	SGPT*	SGOT*	GGT\$	Alkaline Phosphatase*	Total Bilirubin&
<b>150mg QD</b>					
% (N)	0/181	<1% (1/192)	<1% (1/183)	0/200	0/201
95% UL	2%3%	3%	2%	2%	
<b>300mg QD</b>					
% (N)	<1% (2/256)	<1% (1/267)	<1% (1/251)	0/278	0/288
95% UL	3%2%	2%	1%	1%	
<b>600mg QD</b>					
% (N)	<1% (1/256)	<1% (1/263)	0/252	0/273	0/287
95% UL	2%2%	2%	1%	1%	

\*: &gt;= 3\*NUL

\$: &gt;=5\*NUL

&amp;&gt;=2 mg/dl.. Note: subject had normal LFT at baseline.

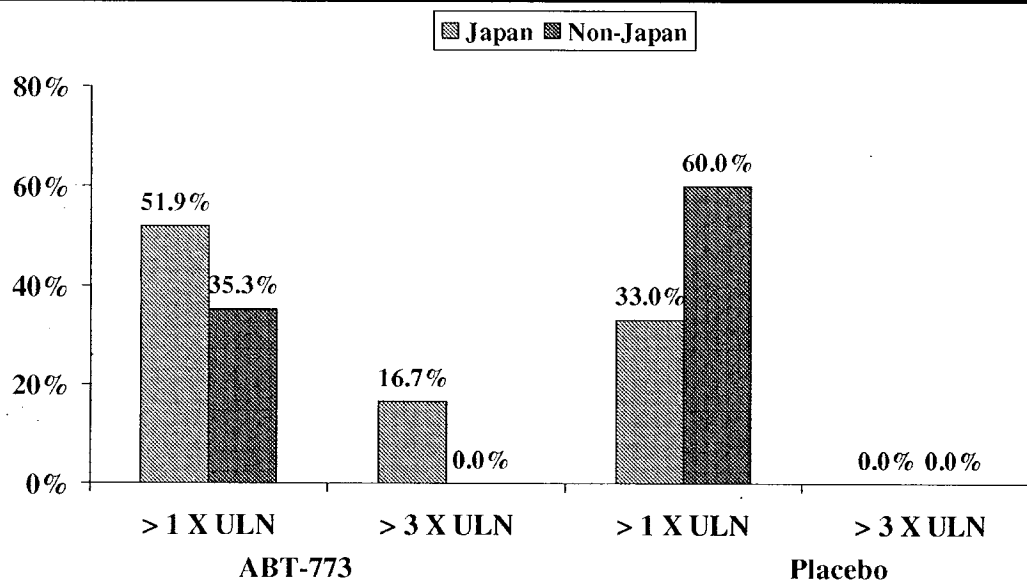


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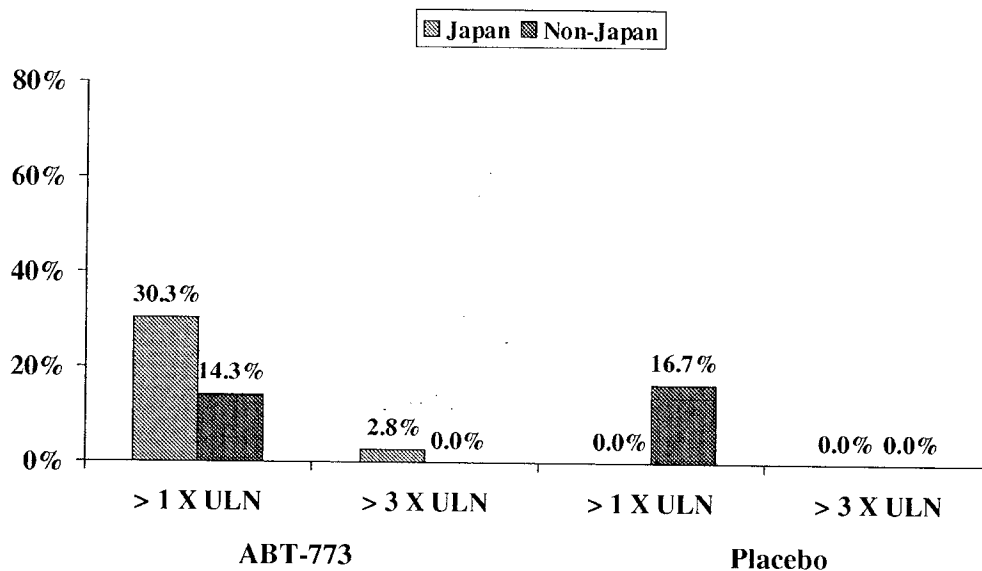
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## Incidence Rate of SGPT Abnormalities Japan Bridging Study



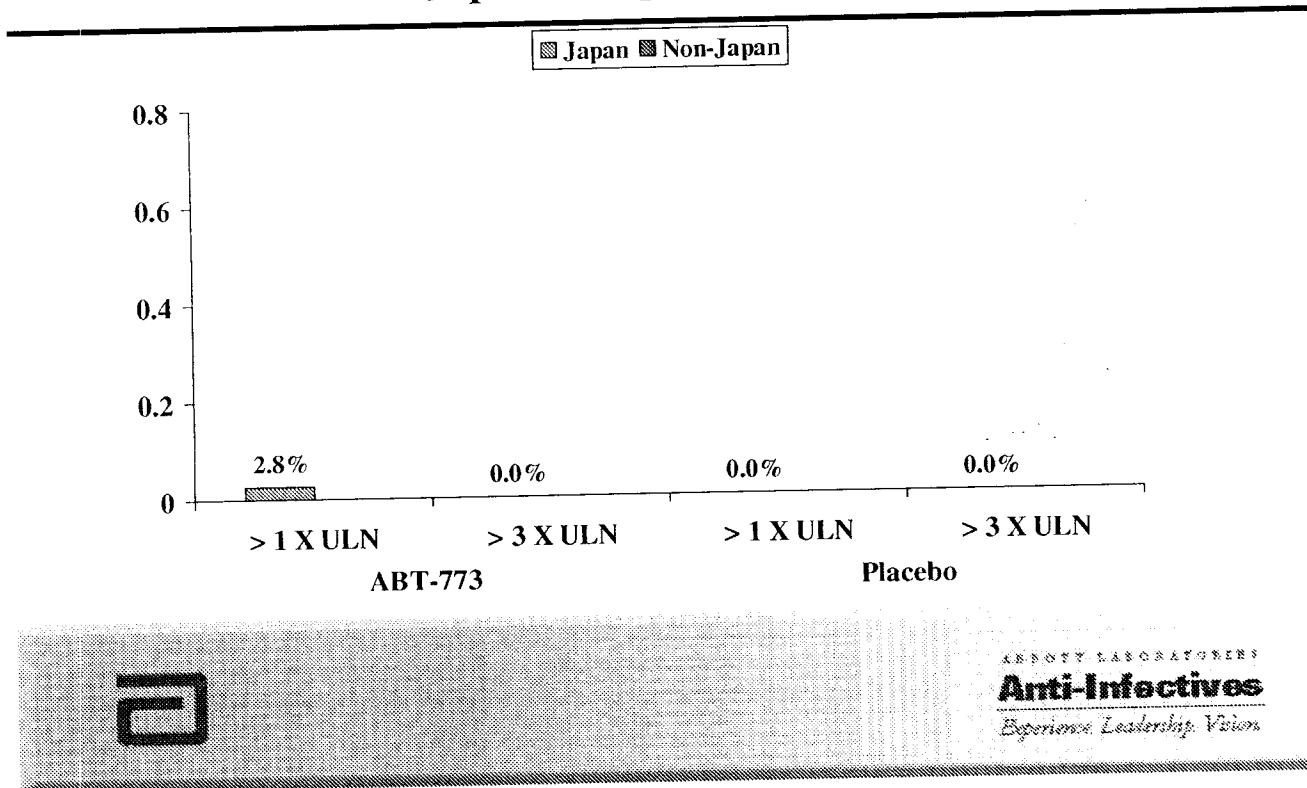
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## Incidence Rate of SGOT Abnormalities Japan Bridging Study



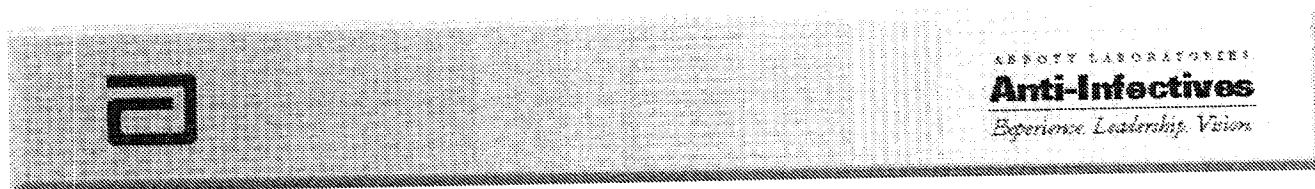
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### Incidence Rate of Bilirubin Abnormalities Japan Bridging Study



**PK Profile**  
**Linda Gustavson**

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***Regulatory  
Jeanne Fox***

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ABBT205225

### ***ABT-773 Regulatory Status***

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- Original U.S. Oral IND submitted 2/2/99
- Phase 3 pivotal trials initiated 11/00
- End-of-Phase 2 Clinical FDA meeting 11/27/00
- End-of-Phase 2 CMC FDA meeting target 1/01
- Tablet NDA submission target 8/02



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ABBT205224

## ***ABT-773 Regulatory Issues***

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- **ABT-773 Potential for QT Prolongation**
  - QT issue is hot button for FDA
  - Question whether ketolides behave like macrolides
  - FDA requested additional dog tox work to evaluate QT
  - Required to include ECG monitoring in pivotal Phase 3 studies
- **ABT-773 Potential for QT Prolongation**
  - telithromycin (Ketek) data residing at FDA
    - Advisory Meeting scheduled for January
- **FDA may require a Phase 1 study in patients with underlying cardiac disease**
- **Some antimicrobials now contain warnings for QT prolongation**



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### ***ABT-773 Regulatory Issues***

---

- **ABT-773 Potential for Liver Toxicity**
  - Ketolides similar to macrolides?
  - Request for additional dog tox work
  - telithromycin (Ketek) data residing at FDA
    - Advisory meeting scheduled for January
- **Plan to conduct routine liver monitoring in all Phase 3 studies**



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# PART 6

## ***ABT-773 Regulatory Issues***

---

- Indication to treat resistant pathogens
- FDA skepticism regarding clinical significance of “macrolide-resistant *S. pneumo*”
- FDA will require “body of evidence”
  - excellent eradication of susceptible organisms
  - > 10 resistant organisms eradicated to include good proportion of bacteremic CAP patients



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## ***ABT-773 Regulatory Issues***

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- **Miscellaneous**

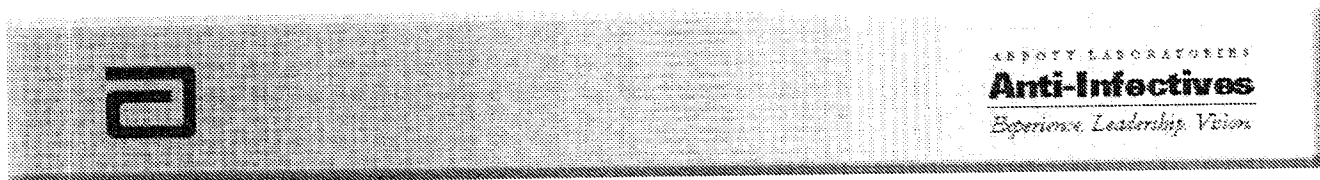
- Based on NDA timing, potential good candidate for E-submission
- Timing of IV program may affect ability to document effectiveness vs. resistant pathogens in bacteremic patients
- Timing of pediatric program and "due diligence" for formulation development critical



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***Commercial Profile, Positioning & Financials***  
***Rod Mittag***

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ABBT205225



***I.V. Program  
Carol Meyer***

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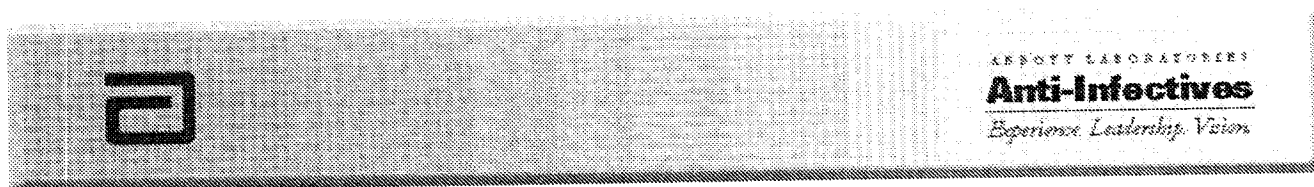
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ABBT205230

**ABT-773 IV Program**  
*Formulation Objectives*

---

- ✧ Reconstituted solution . Once a day dosing. Low pain on injection
- ✧ Lyophilized powder, consisting of ABT-773 and a counterion base.
- ✧ One strength, in a flip-top vial and the ADD Vantage system at launch.
- ✧ Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.

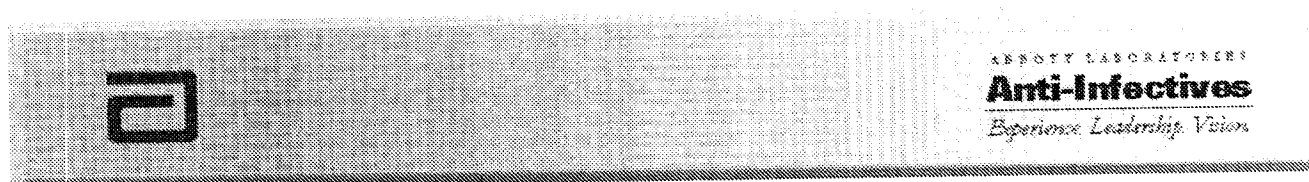


## **ABT-773 IV Formulation**

*Status*

---

- **PPD funded Program 01/00-08/00 (\$1.4MM)**
  - Formulation development ( lactate salt, lyophilized powder)
  - Animal pain models
  - Two week Tox study (monkey)
- **HPD funded Program 08/00-12/00 (\$0.8MM)**
  - Two week Tox study (rat)
  - Clinical supplies for Phase I
  - Stability program



***ABT-773 IV Formulation***  
Animal Pain Study Results

---

- Assessed 6 prototypes( 3 different counterions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
- Results not conclusive
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



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**ABT-773 IV**  
*Planned Clinical Program*

---

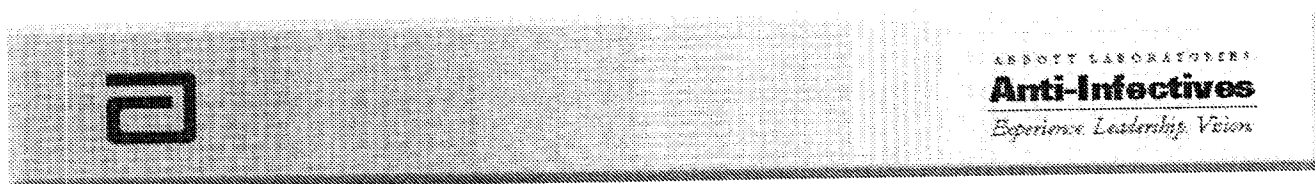
- Single Dose -rising Phase I study
- Multiple Dose Phase I with selected dose
- Initiate Phase III
  - 2 step-down CAP studies (US/Europe)
  - 2-3 days dosing
  - Two seasons to complete
- Filing

Mar/01

June/01

Oct/01

Aug/03



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ABBT205234

## ***ABT 773 IV Program*** ***Summary***

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- **Comments**

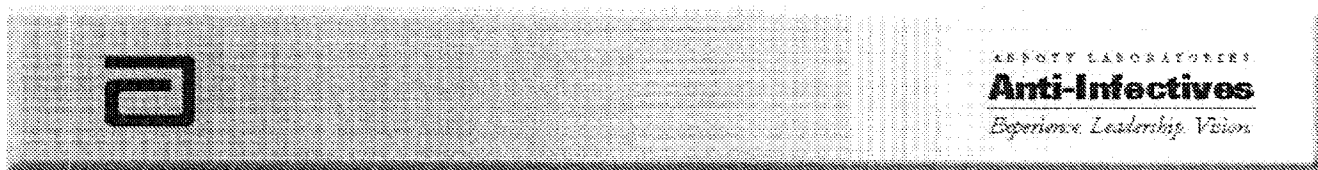
- Funding for '01 not available with PPD/HPD
- Go/No go could be made after Phase I based on safety profile(pain,QT,GI)
- Milestone funding recommended (\$MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant S. pneumo claim



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***Pediatric Program***  
*Carol Meyer*

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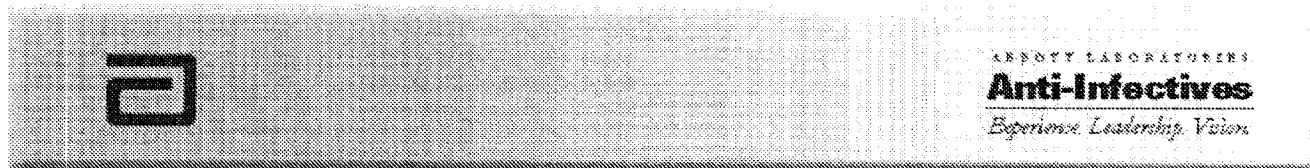
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**ABT-773 Pediatric Program**  
*Formulation Objectives*

---

- **Develop coated particle formulae for global use**
  - Formulate coated particles for Suspension - 150mg/5mL & 300mg/5mL
  - Formulate coated particles as a dry syrup, sprinkle or sachet.
- **Desired Properties**
  - Once a Day Dosing
  - Acceptable 'Initial Taste'
  - Minimal 'After Taste'
  - No Unpleasant Mouth-feel
  - Acceptable Color and Flavor
  - No Refrigeration Required.





### ***ABT-773 Pediatric Program***

*Status*

---

- Initiated January 2000
- 2000 Funding through first PK study milestone only (\$MM)
- Prototype Development completed (granules for suspension) May '00
- Phase I Single Dose Study - 2 prototypes completed Aug '00
- First set of Taste Evaluations completed Sep/00
- Comparative Taste vs Clari and Azi Dec/00



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***ABT-773 Pediatric Program***  
*Formulation Trade-off*

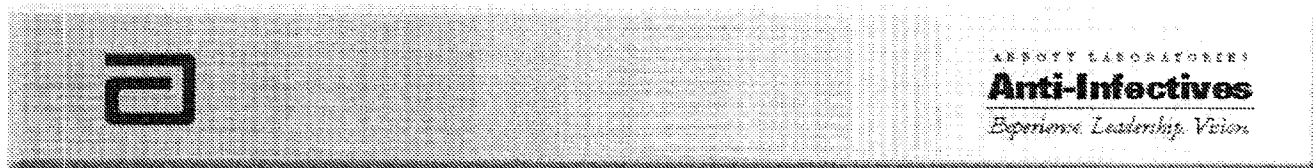
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ABT-773 Pediatric - Reconstitutable Suspension

Taste / Cost



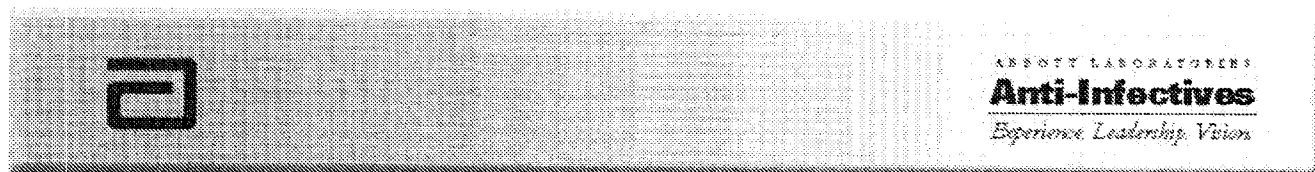
Bioavailability



### ***ABT 773 Pediatric Program*** ***Challenges***

---

- **Pharmacokinetic Profile (plasma,middle ear fluid)**
- **Taste**
  - Masking Bitter Taste
  - Flavor
  - Mouth-Feel
- **Preserving the Reconstituted Suspension**
- **Ease of Manufacture**
- **Cost**



## ***ABT 773 Pediatric Program***

### ***Formulation Development***

---

- **Formula Selected**

- Zein Coated Stearine 07 Based Particles
- Formula acceptable both from an Organoleptic and Dog Bioavailability standpoint
- Two prototypes
  - Same core
  - Different coating levels (15% and 25% coating)

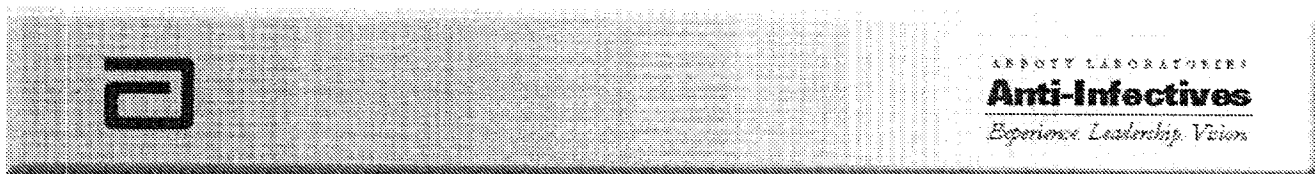


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***ABT 773 Pediatric Program***  
Taste Assessment

---

- **Taste Assessment conducted by Arthur D Little**
  - Utilized a Flavor Profile Method of Sensory Analysis
- **Task 1: Sensory Analysis of Aqueous Solutions/ Suspensions of Uncoated Drug Substances**
  - ABT-773
  - Clarithromycin (Biaxin®)
  - Azithromycin (Zithromax®)
- **Task 2: Sensory Analysis of Coated ABT-773 Prototypes**



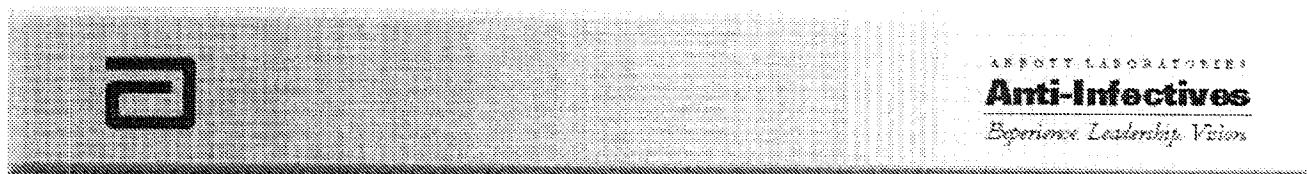
**ABT 773 Pediatric Program**  
Taste Assessment

**Sensory Analysis of Uncoated Drugs**  
*Summary of Results*

*The three drug substances can be ranked from most to least bitter as follows:*

Drug Substance	Concentration (ppm) Which Exhibits an Initial Bitter Intensity $\leq 1$ (Slight)
ABT-773	0.79
Clarithromycin	4.2
Azithromycin	15

- ABT-773 is approximately five times more bitter than clarithromycin



***ABT 773 Pediatric Program***  
Taste Assessment

---

- **The flavor quality of the two coated drug prototypes was similar—the bitter intensity was moderate-to-strong initially and throughout the aftertaste.**
  - The observed bitter intensity is well above the “consumer concern level” of a slight intensity.
  - We believe that the lingering bitterness results from the “sustained release” of drug from the coated drug particles that lodge in the oral cavity (both prototypes exhibited a moderate amount of grittiness).



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**ABT 773 Pediatric Program**  
Phase I PK Results

- The AUC ratio (suspension:tablet) is 75% and the Cmax ratio is 77 to 79% for the two suspension formulations (SC-1a and SC-1b) respectively.

Pharmacokinetic Parameters	Tablet (N = 42)	Suspension (SC-1a) (N = 41)	Suspension (SC-1b) (N = 41)
Tmax (h)	3.0 ± 1.3	2.6 ± 1.0	2.8 ± 1.0
Cmax (ng/mL)	628 ± 263	505 ± 234	494 ± 223
AUC <sub>∞</sub> (ng•h/mL)	4527 ± 1830	3645 ± 2226	3521 ± 1868
t <sub>1/2</sub> (h)‡	6.3	6.8	6.7
Cmax Ratio (test/ref)*	---	0.79	0.77
AUC <sub>∞</sub> Ratio (test/ref)*	---	0.75	0.75

‡ Harmonic mean.

\* Geometric mean



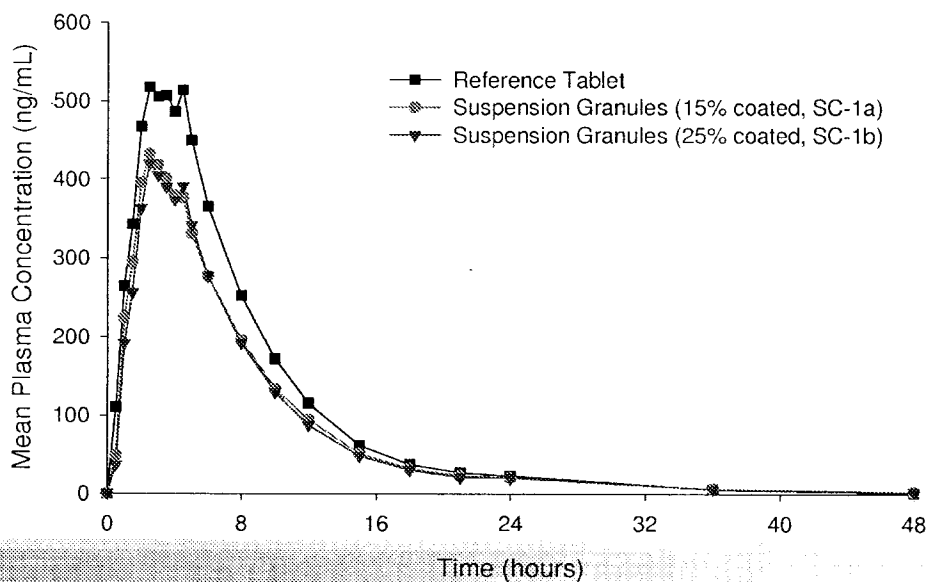
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## ABT 773 Pediatric Program

Phase I PK Results

Study M00-196: Preliminary Mean ABT-773 Plasma Concentration-Time Profiles



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**ABT 773 Pediatric Program**  
Proposed Clinical Program

Proposed Pediatric Clinical Studies for Registration (Phase 1, 2, 3)			
Indications/Type	Phase	No. of Studies	No. of Subjects
PK adult single rising dose, multiple rising dose/effect of food	1a 1b	4	96
Otitis Media (dose ranging), PK in children	2	1	100
Otitis Media, Pharyngitis, CAP	3	6	1800



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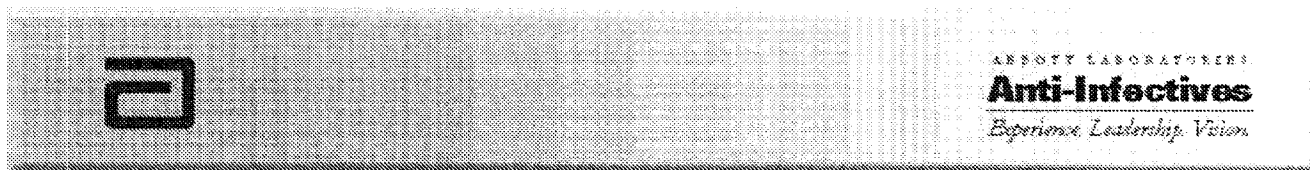
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***ABT 773 Pediatric Program***  
Proposed Clinical Program

---

- **First option**
  - Develop a pro-drug with no immediate after taste , stable in a suspension formulation , hydrolyzed in acidic pH and absorbed as parent drug.
  - Three pro-drugs under study (benzoyl,TMB,ES)
- **Second option**
  - Continue improving after taste,PK of parent drug formulation.
- **Recommend first option with Go/No go in 06/01 (\$MM)**



***Japan Program***  
*Carol Meyer*

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**Japan Program**  
*Taisho*

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- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan
- Findings in first PK trial in Hawaii resulted in repeat of Phase I in Japan



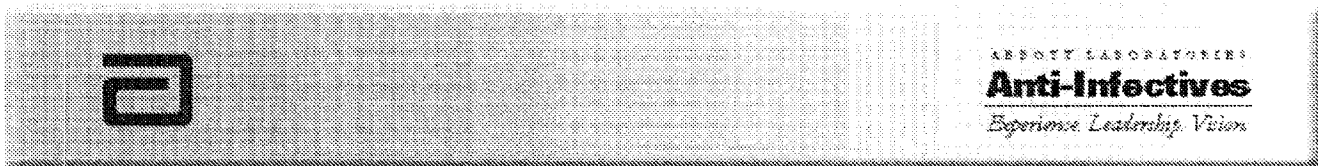
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## ***Japan Program***

### ***Phase I Findings***

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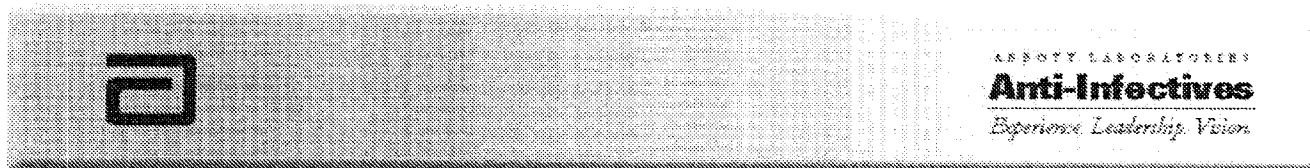
- Initial Phase I study conducted in Hawaii with Japanese and non-Japanese subjects
- Results indicate 50% higher AUC and Cmax in Japanese vs non-Japanese
- Liver enzyme elevations were noted in a few Japanese subjects, however it was not dose related
- Decision made to repeat Phase I in Japan



**Japan Program**  
*Clinical Plan*

---

<b>• Phase I in Japan</b>	<b><u>Start</u></b>
– Food Effect Study	Nov/00
– Single and multiple dose study	Dec/00
– Review data (Abbott/Taisho) <ul style="list-style-type: none"><li>• PK data Japanese vs Caucasian</li><li>• Development program strategy</li></ul>	April/01
– Present Kiko data and recommend development program	May/01
– Start Tissue Conc. Study	2Q/01



## ***Japan Program***

### ***Clinical Plan***

---

- **PK similar in Japanese and Caucasians (12/02 filing)**
- **Recommend to Kiko same dose in Japan as in ex-Japan**
  - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in SSS, Dentistry, Otolaryngology, UTI and pan- bronchiolitis
  - Taisho agreement necessary prior to Kiko meeting
- **PK different in Japanese and Caucasians(12/03 filing)**
  - Phase II dose ranging study in CAP (Bridging study)
  - -Phase III comparative study will be required
  - Full development time line
  - Implications on Taisho cost-sharing

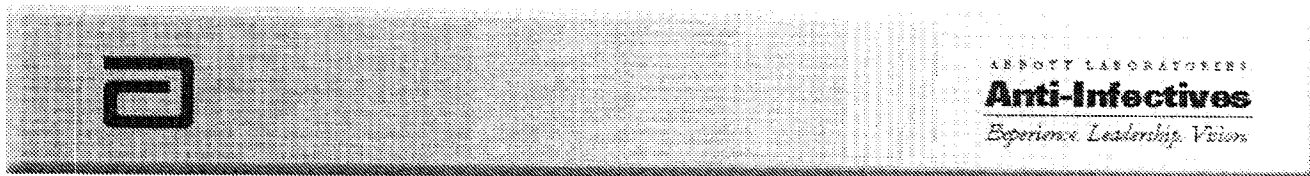


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**Summary**  
*Carl Craft*

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## *Backups*

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Competitive Update, Ketek-Rod Mittag  
OS/IV/overall financials-Rod Mittag

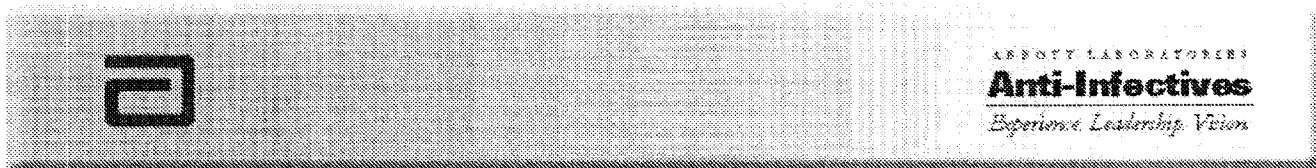


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***IV/OS/Overall Financials***

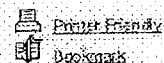
**Rod Mittag**



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Meeting: 2001 ASCO Annual MeetingCategory: Lung CancerSubCategory: Non-Small-Cell Lung Cancer

### Phase III Study of the Matrix Metalloprotease (MMP) Inhibitor Prinomastat in Patients Having Advanced Non-Small Cell Lung Cancer (NSCLC).

Abstract No: 1226

Author(s): Michael Smylie, Richard Mercier, David Aboulafia, Robert Tucker, Philip Bonomi, Mary Collier, Mary Rose Kelier, Jill Stuart-Smith, Mark Knowles, Neil J. Clendinning, Frances Shepherd, Cross Cancer Institute, Edmonton, Canada; Marshfield Clinic, Marshfield, WI; Virginia Mason Medical Center, Seattle, WA; Wake Forest University, Winston Salem, NC; Rush University, Chicago, IL; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA; Princess Margaret Hospital, Toronto, Canada.

Abstract: MMPs degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG3540) is a potent inhibitor of MMPs that demonstrated efficacy in in vivo tumor models. A phase III study investigated prinomastat in combination with paclitaxel (P) and carboplatin (C) in chemotherapy naive patients (pts) having NSCLC. P (200 mg/m<sup>2</sup> over 3 hours) and C (AUC6) were administered q3weeks. Pts were randomized to prinomastat 5mg (dose-ranging arm), 10mg or 15mg, or placebo, orally twice daily. Between 3/98 and 9/99, 686 pts were enrolled; interim results are available for 677 pts. Baseline characteristics were balanced with median age 62 years, 62% male, 85% WHO PS 0/1, 56% adenocarcinoma, 12.6% stage IIIB(T4), 74% stage IV, 11.8% recurrent disease, and 84% measurable disease. P+C dose-intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and, rarely, tendinous contracture. Grade-2 events occurred in 16, 19, 22 and 31% of pts in placebo, 5, 10 and 15mg arms, respectively. Grade-2 MS persisting for 3 weeks were managed by treatment-rest and prinomastat dose reduction. No differences were observed among the treatment arms in overall (OS) or 1-year survival, progression-free survival (PFS), symptomatic PFS (SPFS) or response rate (RR). Efficacy was not enhanced by the addition of prinomastat to P+C in pts having advanced NSCLC.



#### Efficacy Parameters

	Patients	RR	Median (months)			1-Yr Survival
			PFS	SPFS	OS	
	Randomized	%				%
P+C- Placebo	198	21	3.5	6.3	10.2	29
P+C- 5mg	84	27	3.6	5.3	9.3	30
P+C- 10mg	197	19	3.3	5.1	8.6	35
P+C- 15mg	198	18	4.3	6.2	9.1	40

Meeting: 2004 ASCO Annual Meeting

Category: Breast Cancer

SubCategory: Metastatic Breast Cancer

 Print Friendly Bookmark


### Phase II Study of the Matrix Metalloprotease Inhibitor Prinomastat in Patients with Progressive Breast Cancer.

Abstract No: 187

Author(s): Hope S. Rugo, Dan Budman, Charles Vogel, Said Baidas, Gina Fleming, Mary Collier, Mary Dixon, Yazdi Pithavala, Neil J. Clendenen, Debajit Tripathy, Dan Hayes, University of California San Francisco, San Francisco, CA; North Shore University Hospital, Manhasset, NY; Columbia Cancer Research Network, Plantation, FL; Lombardi Cancer Center, Georgetown University, Washington, DC; University of Chicago, Chicago, IL; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA

Abstract: Matrix metalloproteases (MMPs) are enzymes that degrade the extracellular matrix. Prinomastat (AG3340) is a potent MMP inhibitor designed using X-ray crystallography that reduced tumor angiogenesis, invasion, and metastasis in preclinical models. Patients (pts) having metastatic breast cancer that progressed on most recent therapy were randomized to 5 or 25 mg prinomastat administered orally twice daily. The rate of stable disease (SD), time to progression (TTP), potential biomarkers of MMP inhibition and the safety of single agent prinomastat were studied. 15 pts were to enroll into each treatment arm with expansion to 30 pts in an arm if at least one pt had SD at 8 weeks. A total of 44 female pts were enrolled, 29 pts received 5 mg and 15 pts received 25 mg prinomastat. Median age was 58 years (range 37-84), 93% of pts had failed chemotherapy in the metastatic setting, 55% had visceral metastases, and 70% had measurable disease. Musculoskeletal effects (hypothesized to be related to MMP inhibition) required treatment rest or discontinuation in 21% of pts at 5 mg between weeks 8-24 and 27% of pts at 25 mg between weeks 4-8. No objective disease responses were observed. Median TTP was 8 weeks in both arms, 9/29 pts in the 5 mg dose arm had SD at week 8, with 5 pts stable for at least 16 weeks. Preliminary analyses indicate that some biomarkers had potential prognostic value or paralleled disease progression. Low pretreatment plasma VEGF ( $<40\text{pg/mL}$ ) and urine pyridinoline levels ( $<90\text{pmol/Micromol creatinine}$ ) correlated with SD at 8 weeks [67% vs 25% ( $p<0.05$ ), and 100% vs 42% ( $p<0.005$ ) for SD vs PD at week 8, respectively]. Further analyses of disease stabilization and correlative studies will be presented.



Meeting: 2001 ASCO Annual MeetingCategory: Genitourinary CancerSubCategory: Prostate Cancer [Printer Friendly](#) [Bookmark](#)

### Interim Results of a Phase III Study of the Matrix Metalloproteinase Inhibitor Prinomastat in Patients Having Metastatic, Hormone Refractory Prostate Cancer (HRPC)

Abstract No: 692

Author(s): Frederick R. Ahmann, Fred Saad, Richard Merzner, Robert A. Huddart, J. Trevor Roberts, Mary Collier, Lei, Anna Bettencourt, Min H Zhang, Neil J. Clendeninn, George Wilding, Arizona Cancer Center, Tucson, AZ; CHUM-Notre Dame, Montreal, Canada; Marshfield Clinic, Marshfield, WI; The Royal Marsden, Sutton, UK; Newcastle General Hospital, Newcastle, UK; Agouron Pharmaceuticals Inc., A Pfizer Company, La Jolla, CA; University of Wisconsin, Madison, WI



**Abstract:** Matrix metalloproteinases (MMPs) degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG3340) is a potent inhibitor of MMPs that demonstrated efficacy in preclinical in vivo tumor models. A phase III trial investigated prinomastat in combination with mitoxantrone (M) and prednisone (P) in chemotherapy naive patients (pts) having metastatic HRPC. M was administered intravenously at 12 mg/m<sup>2</sup> q3weeks and P orally, 5mg twice daily. Pts were randomized to 5 or 10mg prinomastat or placebo, orally twice daily. Between 4/98 and 7/00, 553 pts were enrolled; interim results are available for 406 pts. Baseline characteristics were balanced with median age 71 years, median PSA 94 ng/mL and 33% measurable disease. M+P dose-intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and, rarely, tendinous contracture. Grade-2 MS were observed in 13, 22 and 22% of pts in the placebo, 5 and 10mg arms, respectively; events persisting for at least 3 weeks were managed by treatment-rest and prinomastat dose reduction. No differences were observed among the treatment arms in PSA response rate (RR, 75% reduction for 3wks); progression-free survival by radiography (RPFS), PSA (50% increase for 3wks), or symptoms (SPFS), or overall (OS) and 1-year survival. Efficacy was not enhanced by the addition of prinomastat to M+P in pts having metastatic HRPC.

#### Efficacy Parameters

	Patients	PSA/RR	Median (months)				1-Year Survival
	Randomized	(%)	RPFS	PSA/PFS	SPFS	OS	(%)
M+P	138	14	6.0	6.8	7.7	14.8	60

M+P- 5mg	134	17	6.0	8.9	8.6	15.1	64
M+P-	134	18	4.7	6.5	8.3	14.7	63



Meeting: 2001 ASCO Annual Meeting Printer FriendlyCategory: Gynecologic Cancer BookmarkSubCategory: Gynecologic Cancer

**An International Multicentre Phase III Study of BAY 12-9566 (BAY) Versus Placebo in Patients (pts) with Advanced Ovarian Cancer (OVCA) Responsive to Primary Surgery/Paclitaxel + Platinum Containing Chemotherapy (CT).**

Abstract No: 843

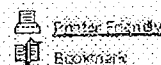
Author(s): Hai W. Hirt, Ignace B. Vergote, John R. Jeffery, Robert N. Grunshaw, Gavin C. Stuart, Cesar Vendicla, Daniel A. Vorchiof, Mark S. Carey, Sabine Cappelletti, Brian Schwartz, Dongsheng Tu, Anna Sadura, Lesley Seymour, Hamilton Regional Cancer Centre, Hamilton, ON, Canada; University Hospital Leuven, Leuven, Belgium; Health Sciences Centre, University of Manitoba, Winnipeg, MB, Canada; Nova Scotia Cancer Centre, Halifax, NS, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Hospital Universitaria, Madrid, Spain; Sandton Oncology Centre, Johannesburg, South Africa; London Regional Cancer Centre, London, ON, Canada; Bayer s.a. - n.v., Bruxelles, Belgium; Bayer, Inc., Toronto, ON, Canada; National Cancer Institute of Canada - Clinical Trials Group, Kingston, ON, Canada; National Cancer Institute of Canada - Clinical Trials Group, Kingston, ON, Canada.

Abstract: BAY is a biphenyl matrix metalloproteinase inhibitor (MMPI) with anti-angiogenic and anti-metastatic properties in vivo. The objective of the study was to determine whether the addition of BAY after optimal response to chemotherapy could improve survival. Pts enrolled in the study had received 6-9 cycles of platinum/paclitaxel containing CT for stage III or IV OVCA, with a response of NED, or complete or partial response with residual disease  $\leq 2$  cm. Pts were then randomized to BAY 800 mg po bid or placebo. The primary endpoint was progression-free survival (PFS), secondary endpoints were quality of life, toxicity, response, and overall survival (OS). The total planned sample size was 780. The study was closed after 243 pts had been randomized because of negative results from other phase III trials in pancreatic and small cell lung cancer. The final analysis was performed in August 2000 after the requisite number of events for the first planned IA had occurred; 54% of patients had progressed and 18% had died. Patient characteristics: performance status was ECOG 0/1/2 in 65/33/2%; median age 57 years; 80% of pts were FIGO stage III; 60% were optimally debulked; 76% had serous histology and 66% had grade 3 histology. Toxicity was generally grade 1 or 2 in severity, with the most common (BAY versus placebo) being nausea (26% versus 13%), fatigue (24% versus 12%), diarrhea (14% versus 10%), rash (12% versus 7%), grade 3/4 thrombocytopenia (3% versus 1%) and grade 3/4 anemia (5% versus 1%). PFS was 10.4 months (8.5-11.5) for BAY and 9.2 months (7.2-13.0) for placebo ( $p=0.67$ ). OS was 13.9 months (12.9-[infinity]) for BAY and 11.9 months (10.5-16.5) for placebo ( $p=0.53$ ). We conclude that BAY was generally well tolerated and although the data are still immature, there is no evidence of an impact of BAY on PFS or OS.

Meeting: 2001 ASCO Annual Meeting

Category: Lung Cancer

SubCategory: Small-Cell Lung Cancer



### Randomized Double-Blind Placebo-Controlled Trial of Marimastat in Patients with Small Cell Lung Cancer (SCLC) Following Response to First-Line Chemotherapy: an NCIC-CTG and EORTC Study.

Abstract No: 11

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**Abstract:** Increased expression of matrix metalloproteinases is associated with poor prognosis in SCLC. Marimastat (M) is an orally available, broad-spectrum matrix metalloproteinase inhibitor that has shown pre-clinical activity in many solid tumors. This trial was undertaken to determine whether adjuvant treatment with M could prolong remission duration and overall survival in patients with SCLC. Patients with documented SCLC and performance status 0-2 were eligible for study if they had achieved CR or PR in response to 1st-line therapy and had life expectancy  $\geq 12$  wks. They were stratified by radiotherapy (early vs late, vs none) stage at diagnosis (extensive vs limited) response (CR vs PR) and cooperative group. They were randomized to receive M 10 mg po bid or placebo 1 capsule po bid for up to 2 yrs. Treatment was stopped for disease progression or toxicity. The study has 80% power to detect a 33% improvement in survival using a 2-sided test. Between 2/97 and 4/00, 555 patients entered the trial. The median duration of follow-up is 20.4 mos and all patients have completed at least 8 mos treatment or have discontinued therapy due to toxicity or relapse. Toxicity was generally limited to musculoskeletal (MS) syndromes (Grade 2, 31%, Grade 3/4, 12%). Dose modifications for MS toxicity were required in 113 patients (20%), and 128 patients (23%) permanently stopped protocol therapy due to toxicity (104 of the 128 stopped for MS toxicity). The median survival for the entire group is 9.5 mos, with 1-yr and 2-yr survivals of 38% and 20% respectively. Survival according to treatment group will be available by May 2001.

#### PATIENT CHARACTERISTICS

	MARIMASTAT (n=277)	PLACEBO (n=278)
<b>NCIC/EORTC</b>	209/68	211/67
<b>Male/Female</b>	164/133	147/131
<b>Age (median)</b>	61.6 years	61.2 years
<b>Limited/Extensive</b>	146/131	137/141
<b>CR/PR/Other</b>	90/174/13	90/184/4

Updated data not available through ASCO abstracts. Study was published; see JCO abstract below:

1: J Clin Oncol. 2002 Nov 15;20(22):4434-9.  
<http://www.jco.org/cgi/content/full/20/22/4434>

Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer.

Shepherd FA, Giaccone G, Seymour L, Debruyne C, Bezjak A, Hirsh V, Smylie M, Rubin S, Martins H, Lamont A, Krzakowski M, Sadura A, Zee B.  
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**PURPOSE:** Increased expression of metalloproteinases is associated with poor prognosis in small-cell lung cancer (SCLC). This trial was undertaken to determine whether adjuvant treatment with the metalloproteinase inhibitor marimastat could prolong survival in responding patients with SCLC after chemotherapy. **PATIENTS AND METHODS:** SCLC patients in complete or partial remission were eligible. They were stratified by radiotherapy (early, late, or none), stage (extensive or limited), response (complete or partial), and cooperative group (National Cancer Institute of Canada-Clinical Trials Group or European Organization for Research and Treatment of Cancer). They were randomized to receive marimastat 10 mg or placebo orally bid for up to 2 years. **RESULTS:** There were 532 eligible patients (266 marimastat and 266 placebo). Stage was limited for 279 patients (52%) and extensive for 253 (48%). Best response to induction therapy was complete remission for 176 patients (33%), partial remission for 341 (64%), and 15 patients (3%) had undergone surgical resection. The median time to progression for marimastat patients was 4.3 months compared with 4.4 months for placebo patients ( $P = .81$ ). Median survivals for marimastat and placebo patients were 9.3 months and 9.7 months, respectively ( $P = .90$ ). Toxicity was generally limited to musculoskeletal symptoms (18% grade  $\geq 3$  for marimastat). Dose modifications for musculoskeletal toxicity were required in 90 patients (33%) on the marimastat arm, and 87 (32%) permanently stopped marimastat because of toxicity. Patients on marimastat had significantly poorer quality of life at 3 and 6 months. **CONCLUSION:** Treatment with marimastat after induction therapy for SCLC did not result in improved survival and had a negative impact on quality of life.

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